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NON-PROTEIN NITROGEN RETENTION DURING ECLAMPSIA AND ALLIED CONDITIONS

THE BLOOD NITROGEN CURVE IN NORMAL AND IN TOXEMIC PREGNANCIES

By E. D. Plass, M. D.

(From the Obstetrical Department of the Johns Hopkins Hospital and University, Baltimore)

An extensive experience with determinations of certain of the non-protein constituents of the blood in the late toxemias of pregnancy has "led us to believe that blood chemical studies are at present of little or no practical assistance in the clinical management of these cases, and that the older methods of examination—urinalysis, blood pressure readings and ophthalmoscopy—yield the most valuable information concerning the patient's condition."[1] This statement was based upon the results of analyses of single blood specimens, while in another place,[2] it was stated that "if blood is drawn at daily intervals during the convalescent period, it will be found that, as recovery proceeds, there is a distinct tendency for the non-protein nitrogen to rise and then to return to normal." This communication is concerned with the presentation of the data upon the basis of which the latter statement was made.

Practically all the work previously reported in this field has been done upon single blood specimens obtained at the time at which the clinical picture was most alarming, and so does not bear directly upon the problem in hand; but, occasionally certain observers have repeated determinations at varying intervals after the subsidence of the symptoms, and have drawn conclusions concerning the behavior of the different blood constituents during convalescence. Thus, Killian and Sherwin[3] say: "A prompt improvement, judged from a clinical standpoint and from the chemical composition of the blood, in most instances follows the evacuation of the uterus." It would appear from their tables that on only three occasions did they examine the blood after delivery, so that their conclusions regarding its return to normal are of very doubtful value. The same criticism can be applied to the work of Williams,[4] who plotted a curve for whole blood uric acid after delivery and remarks that "delivery and recovery from the symptoms are associated with a gradual return of the uric acid in the blood to its normal amount." Apparently, no one patient was studied on successive days and the

conclusions drawn are scarcely warranted by the facts advanced in their support. Caldwell and Lyle [5] believe that "when the nitrogenous constituents do not return to normal early in convalescence, a doubtful prognosis for subsequent pregnancies is justified." An examination of their protocols shows that, when the blood was analyzed for the second time within forty-eight hours after delivery or after an amelioration of the symptoms, (Cases 1 and 10), there was a higher concentration of the various nitrogenous materials than at the first examination. No attention was, however, paid to this finding, which is so nearly in line with our own.

Moreover, Morse,[6] in the course of his amino-acid studies, noticed that "occasionally, in my series, values slightly higher than normal were associated with the period of convalescence. Thus, in Case 18, there was a progressive increase in the amino-acid nitrogen during the first and second days after delivery." Brown [7] has evidently experienced a similar alteration, for he says: "I have found so many times cases of impending eclampsia coming on without much evidence of increased toxemia as shown by the blood chemistry and yet after they have gone through seizures or after they begin to get well the nitrogen retention increases. Our pathologist has come to the conclusion that the blood chemistry lags. Apparently the clinical picture is twenty-four hours ahead of the blood chemistry." These remarks were made impromptu during a discussion, and no figures are offered to substantiate them.

Hellmuth,[8] in his Cases 3, 5, 6 and 7, found that the non-protein fractions in the blood tend to increase during the first twenty-four hours after delivery in eclamptic patients, but laid no particular stress upon the finding. Walthard [9] (1922) also noted this tendency and says: "Im Wochenbett besteht kurz post partum noch eine Erhöhung des Rest N-Spiegels. Er sinkt indessen bald frühèr, bald später, und erreicht schliesslich wieder die Norm." More recently, Stander [10] has reported a series of observations upon the blood of toxemic women, in many of whom he made repeated determinations of the various non-protein nitrogenous constituents. The specimens were not collected at any particular intervals, but in several instances his protocols would indicate that he found an increase in these non-protein fractions after delivery and clinical improvement.

Experimental

Blood specimens were obtained for study from 10 non-convulsive toxemic and 7 eclamptic patients, while 7 normal women were studied during labor and the early puerperium, in order that something might be learned of the normal variations. This necessitated analyses of 182 samples of whole blood and plasma. As a rule, oxalated plasma rather than whole blood was utilized, because of our feeling that the fluid portion of the blood is more directly concerned with problems of retention and elimination.[11] In a few instances, however, simultaneous determinations of whole blood were done. The blood samples were obtained by venepuncture, without particular reference to meals, and coagulation was prevented by the use of powdered potassium oxalate in small quantities. Whenever possible, the analyses were carried out immediately, but when the blood was collected at night, it was preserved in the ice-box until the following morning, and then after thorough centrifugalization, the clear plasma was siphoned off the sedimented cells. The micro-methods of Folin and Wu [12] were used for the non-protein nitrogen, urea nitrogen and uric acid, and proved most satisfactory. The total nitrogen of the plasma was determined on 1 c.c. portions by the regular Kjeldahl procedure, and, after subtracting the total non-protein fraction, the plasma protein percentage was obtained by the use of the factor 6.25. All analyses were made in duplicate and when unsatisfactory results were obtained new determinations were done. Frequent checks were made upon the uric acid standard, which was found to deteriorate rather rapidly.

The portion of the work which relates to the plasma proteins was really done as a part of a comprehensive investigation of this subject in normal and abnormal pregnancies. The complete results of this study appear in the next article in this *Bulletin*. The plasma protein values cited here merely serve to indicate that the non-protein nitrogen variations detected are not dependent upon changes in plasma concentration.

Results

The complete results are presented in tabular form, while Figures 1, 2, 3, and 4 are graphic representations of the variations in selected illustrative cases. A brief résumé of the clinical aspects of each case is given in the appendix * under the appropriate case number.

Normal Pregnancy

Cases 1 to 7 were apparently normal pregnant women who were delivered practically at full term, 5 spontaneously, 1 by low forceps and 1 by radical Cesarean section. In no case was the labor prolonged (more than 30 hrs.), and the blood lost at delivery was uniformly within normal limits (100 to 560 c.c.). In 6 cases chloroform was given and in one case no anesthetic was administered. The following tables give the results in detail.

* The appendix, because of its length, will not be included here, but will appear in the reprints.

CASE 1.

Normal. Hosp. No. 10574. Col. 22. 1 child.

DATE—1920	Total* N. P. N. Mg. per 100 c.c.	Urea* N. Mg. per 100 c.c.	Urea N.† / N. P. N. Per cent	Uric acid Mg. per 100 c.c.	Plasma protein Per cent	Albumin in urine G. per L.	Systolic B. P. MM.	REMARKS
June 9—10.30 A. M.	17	11	62	2.8	7.32	0	100	On admission. 10th month of pregnancy.
June 29— 8.20 A. M.	15	9	61	2.6	5.36	0	—	In labor, 2nd stage, 1 hr. 25 min. a. p.
Delivered June 29—9.45 A. M.								
June 30— 9.15 A. M.	21	15	74	3.9	6.53	0	—	24 hours p. p.
July 1— 9.00 A. M.	20	13	66	4.2	5.87	0	—	48 hours p. p.
July 2— 9.30 A. M.	20	14	72	2.9	5.96	0	—	72 hours p. p.
July 3— 9.30 A. M.	20	12	58	2.6	5.83	0	—	96 hours p. p.

* Total N. P. N. and Urea N. values are given in the nearest whole number.

† The Urea N : N. P. N. ratio is computed using values calculated to the first decimal place. Consequently, the value given is frequently not that obtained from the Urea N. and N. P. N. values here recorded.

CASE 2.

Normal. Hosp. No. 10792. Col. 28. 2 children.

DATE—1920	Total N. P. N. Mg. per 100 c.c.	Urea N. Mg. per 100 c.c.	Urea N. / N. P. N. Per cent	Uric acid Mg. per 100 c.c.	Plasma protein Per cent	Albumin in urine G. per L.	Systolic B. P. MM.	REMARKS
Nov. 9— 8.10 A. M.	17	12	71	1.8	6.83	tr.	122	Not in labor, 50 min. before delivery by elective C. S. followed by hysterectomy.
Delivered Nov. 9—9.00 A. M.								
Nov. 10— 9.30 A. M.	19	14	73	1.2	6.68	tr.	—	24 hours p. p.
Nov. 11— 9.30 A. M.	19	11	55	0.8	6.77	tr.	—	48 hours p. p.
Nov. 12—10.30 A. M.	19	12	62	0.5	6.99	tr.	—	3 days p. p.
Nov. 13— 9.00 A. M.	20	8	37	0.8	6.89	tr.	—	4 days p. p.
Nov. 14—10.00 A. M.	19	9	46	0.9	6.54	tr.	—	5 days p. p.
Nov. 15—12 Noon	17	8	48	0.7	6.65	tr.	—	6 days p. p.

CASE 2.

Normal. Hosp. No. 10792. Col. 28. 2 children.

Whole Blood

DATE—1920	Total N. P. N. Mg. per 100 c.c.	Urea N. Mg. per 100 c.c.	Urea N. / N. P. N. Per cent	Uric acid Mg. per 100 c.c.	Blood protein Per cent	Albumin in urine G. per L.	Systolic B. P. MM.	REMARKS
Nov. 9— 8.10 A. M.	23	11	48	1.5	18.24	tr.	122	Not in labor, 50 min. before delivery by elective C. S. followed by hysterectomy.
Delivered Nov. 9—9.00 A. M.								
Nov. 10— 9.30 A. M.	24	13	53	1.4	18.34	tr.	—	24 hours p. p.
Nov. 11— 9.30 A. M.	27	10	39	0.9	17.72	tr.	—	48 hours p. p.
Nov. 12—10.30 A. M.	21	11	53	0.6	17.84	tr.	—	3 days p. p.
Nov. 13— 9.00 A. M.	23	10	41	0.7	17.48	tr.	—	4 days p. p.
Nov. 14—10.00 A. M.	24	11	47	0.8	16.80	tr.	—	5 days p. p.
Nov. 15—12 Noon	23	10	43	0.8	17.34	tr.	—	6 days p. p.

CASE 3.

Normal. Hosp. No. 11432. Col. 19. Primigravida.

Delivered Oct. 20—8.00 A. M.

DATE—1921	Total N. P. N. Mg. per 100 c.c.	Urea N. Mg. per 100 c.c.	Urea N. / N. P. N. Per cent	Uric acid Mg. per 100 c.c.	Plasma protein Per cent	Albumin in urine G. per L.	Systolic B. P. MM.	REMARKS
Oct. 20—10.00 A. M.	22	9	39	5.2	—	0	—	2 hours p. p.
Oct. 21—10.00 A. M.	23	12	50	4.6	7.21	0	—	26 hours p. p.
Oct. 22— 9.00 A. M.	27	13	47	4.5	5.96	0	—	49 hours p. p.
Oct. 23— 9.30 A. M.	22	10	44	3.9	6.35	0	—	3 days p. p.
Oct. 24—11.00 A. M.	24	11	46	3.8	6.25	0	—	4 days p. p.
Oct. 25—10.00 A. M.	24	11	47	3.4	6.33	0	—	5 days p. p.
Oct. 26— 9.30 A. M.	24	10	43	3.1	7.94	0	—	6 days p. p.

CASE 4.

Normal. Hosp. No. 11433. Col. 15. Primigravida.

DATE—1921	Total N. P. N. Mg. per 100 c.c.	Urea N. Mg. per 100 c.c.	Urea N. / N. P. N. Per cent	Uric acid Mg. per 100 c.c.	Plasma protein Per cent	Albumin in urine G. per L.	Systolic B. P. MM.	REMARKS
Oct. 25— 2.20 P. M.	14	7	53	2.1	6.89	0	120	In labor, 1st stage. 15 hours a. p.
Delivered Oct. 26—5.00 A. M.								
Oct. 26—10.00 A. M.	17	10	60	2.2	7.61	0	—	5 hours p. p.
Oct. 27— 9.30 A. M.	19	9	48	2.4	7.23	0	—	29 hours p. p.
Oct. 28—10.00 A. M.	19	8	42	2.8	6.80	0	—	53 hours p. p.
Oct. 29—10.00 A. M.	18	8	44	2.2	7.23	0	—	3 days p. p.
Oct. 30— 9.30 A. M.	19	10	54	1.9	6.80	0	—	4 days p. p.
Oct. 31—10.00 A. M.	19	11	57	1.4	7.43	0	—	5 days p. p.

CASE 5.

Normal. Hosp. No. 11435. Col. 21. Primigravida.

DATE—1921	Total N. P. N. Mg. per 100 c.c.	Urea N. Mg. per 100 c.c.	Urea N. / N. P. N. Per cent	Uric acid Mg. per 100 c.c.	Plasma protein Per cent	Albumin in urine G. per L.	Systolic B. P. MM.	REMARKS
Nov. 1— 2.30 P. M.	17	9	56	1.4	6.81	+ +	115	In labor, 2nd stage. 30 minutes a. p.
Delivered Nov. 1—3.00 P. M.								
Nov. 2—11.00 A.M.	23	11	47	1.8	7.14	+	—	20 hours p. p.
Nov. 3— 9.00 A. M.	21	12	57	2.2	6.03	—	—	42 hours p. p.
Nov. 4—11.00 A. M.	22	13	59	1.9	6.10	—	—	3 days p. p.
Nov. 5— 9.00 A. M.	25	11	44	1.9	6.48	—	—	4 days p. p.

CASE 6.

Normal. Hosp. No. 11501. Col. 18. Primigravida.

DATE—1921	Total N. P. N. Mg. per 100 c.c.	Urea N. Mg. per 100 c.c.	Urea N. / N. P. N. Per cent	Uric acid Mg. per 100 c.c.	Plasma protein Per cent	Albumin in urine G. per L.	Systolic B. P. MM.	REMARKS
Dec. 1— 1.15 P. M.	16	7	44	1.4	7.56	0	140	In labor, 1st stage. 15 hours a. p.
Delivered Dec. 2—4.30 A. M.								
Dec. 2— 9.00 A. M.	19	8	42	1.7	6.27	0	—	4 hours p. p.
Dec. 3— 9.45 A. M.	19	10	54	1.4	6.43	0	—	29 hours p. p.
Dec. 4— 9.30 A. M.	20	10	52	1.3	6.94	0	—	53 hours p. p.
Dec. 5— 9.30 A. M.	23	11	47	0.8	—	0	—	3 days p. p.
Dec. 7— 2.15 P. M.	22	11	52	1.5	—	0	—	5 days p. p.

CASE 7.

Normal. Hosp. No. 11515. Col. 23. Primigravida.

DATE—1921	Total N. P. N. Mg. per 100 c.c.	Urea N. Mg. per 100 c.c.	Urea N. / N. P. N. Per cent	Uric acid Mg. per 100 c.c.	Plasma protein Per cent	Albumin in urine G. per L.	Systolic B. P. MM.	REMARKS
Dec. 10— 9.30 A. M.	19	10	52	2.8	7.47	0	120	In labor, 1st stage. 7 hours a. p.
Delivered Dec. 10—4.00 P. M.								
Dec. 11— 9.30 A. M.	29	17	59	3.3	6.83	0	—	17 hours p. p.
Dec. 12— 9.45 A. M.	31	16	51	3.5	6.08	0	—	41 hours p. p.
Dec. 13— 9.30 A. M.	26	13	51	3.0	7.39	0	—	3 days p. p.
Dec. 17— 9.20 A. M.	23	10	46	2.8	7.73	0	—	7 days p. p.

CASE 8.

Mild pre-eclamptic toxemia. Hosp. No. 10540. White 22. Primigravida.

DATE—1920	Total N. P. N. Mg. per 100 c.c.	Urea N. Mg. per 100 c.c.	Urea N. / N. P. N. Per cent	Uric acid Mg. per 100 c.c.	Plasma protein Per cent	Albumin in urine G. per L.	Systolic B. P. MM.	REMARKS
June 10— 5.00 A. M.	23	15	67	4.7	6.46	tr.	175	Shortly after admission. Not in labor.
Delivered June 11—6.45 A. M.								
June 11— 7.00 A. M.	25	16	64	4.1	7.04	tr.	160	15 minutes after delivery.
June 12— 9.30 A. M.	25	17	68	5.4	6.54	tr.	150	27 hours p. p.
June 13—10.15 A. M.	24	14	60	3.9	6.38	0	150	52 hours p. p.
June 14— 9.30 A. M.	21	14	65	3.6	7.14	0	140	3 days p. p.
June 22— 9.30 A. M.	22	13	61	3.7	7.52	0	134	11 days p. p.

CASE 9.

Severe nephritic toxemia without convulsions—prompt recovery. Hosp. No. 10579. White 35. Primigravida.

DATE—1920	Total N. P. N. Mg. per 100 c.c.	Urea N. Mg. per 100 c.c.	Urea N. / N. P. N. Per cent	Uric acid Mg. per 100 c.c.	Plasma protein Per cent	Albumin in urine G. per L.	Systolic B. P. MM.	REMARKS
June 24— 9.00 A. M.	19	14	74	3.7	6.63	6.0	200	After treatment for 1 day. Not in labor.
Delivered June 24—9.00 P. M.								
June 26—10.00 A. M.	58	47	81	10.0	6.48	4.0	180	37 hours p. p.
June 27—10.00 A. M.	61	50	81	10.4	6.06	1.25	190	61 hours p. p.
June 28— 9.30 A. M.	59	47	80	9.1	7.01	0.3	185	3 days p. p.
June 29— 9.30 A. M.	50	35	70	7.6	6.08	0.3	180	4 days p. p.
June 30— 9.30 A. M.	35	27	78	6.3	6.98	0.25	175	5 days p. p.
July 1— 9.00 A. M.	31	23	74	5.8	7.30	—	—	6 days p. p.
July 2— 9.15 A. M.	28	23	81	5.5	6.80	—	—	7 days p. p.
July 14—11.30 A. M.	24	16	66	4.4	8.02	0.25	145	19 days p. p.
1921 Nov. 15— 3.00 P. M.	33	24	73	1.3	8.46	tr.	170	15 months after delivery.

CASE 10.

Severe pre-eclamptic toxemia—prompt recovery. Hosp. No. 10615. Col. 18. Primigravida.

DATE—1920	Total N. P. N. Mg. per 100 c.c.	Urea N. Mg. per 100 c.c.	Urea N. / N. P. N. Per cent	Uric acid Mg. per 100 c.c.	Plasma protein Per cent	Albumin in urine G. per L.	Systolic B. P. MM.	REMARKS
July 13—12.30 P. M.	17	11	64	3.1	5.71	2.0	180	Day after admission.
July 16— 9.00 A. M.	23	17	76	4.3	5.85	1.0	140	Slight improvement.
July 17—10.00 A. M.	26	21	80	7.6	5.48	—	160	Early in labor.
Delivered July 19—1.30 A. M.								
July 19— 9.30 A. M.	36	29	80	9.7	5.63	—	105	8 hours p. p.
July 20— 8.30 A. M.	46	37	79	11.0	4.99	—	120	31 hours p. p.
July 21— 9.30 A. M.	27	19	69	1.7	5.69	—	120	56 hours p. p.
July 22—10.30 A. M.	21	15	70	0.9	5.91	0.5	120	3 days p. p.
Aug. 2— 5.30 P. M.	23	13	54	2.3	7.60	0.25	130	On discharge. 15 days p. p.
1921 Feb. 7—	24	—	—	—	—	—	—	6 months later.

CASE 11.

Mild pre-eclamptic toxemia—prompt recovery. Hosp. No. 10730. White 18. Primigravida.

DATE—1920	Total N. P. N. Mg. per 100 c.c.	Urea N. Mg. per 100 c.c.	Urea N. / N. P. N. Per cent	Uric acid Mg. per 100 c.c.	Plasma protein Per cent	Albumin in urine G. per L.	Systolic B. P. MM.	REMARKS
Sept. 30— 9.00 P. M.	14	9	61	2.9	6.32	2.0	145	On admission.
Delivered Oct. 2—1.45 A. M.								
Oct. 2— 9.30 A. M.	24	18	77	4.1	6.33	1.0	125	8 hours p. p.
Oct. 3— 9.15 A. M.	26	21	79	4.1	6.32	—	—	32 hours p. p.
Oct. 4— 9.00 A. M.	22	18	82	3.1	6.08	0.5	125	56 hours p. p.
Oct. 5— 9.15 A. M.	24	16	65	3.3	6.62	—	—	3 days p. p.
Oct. 6— 9.30 A. M.	23	17	74	2.8	7.64	—	—	4 days p. p.
Oct. 13— 9.00 A. M.	17	10	57	1.8	7.68	ft. tr.	100	11 days p. p.
Oct. 16— 9.30 A. M.	19	10	51	1.8	7.53	—	—	14 days p. p. on discharge.

CASE 12.

Severe pre-eclamptic toxemia, slow recovery. Hosp. No. 10741. Col. 16. Primigravida.

DATE—1920	Total N. P. N. Mg. per 100 c.c.	Urea N. Mg. per 100 c.c.	Urea N. / N. P. N. Per cent	Uric acid Mg. per 100 c.c.	Plasma protein Per cent	Albumin in urine G. per L.	Systolic B. P. MM.	REMARKS
Sept. 30— 9.00 P. M.	18	13	74	4.5	5.57	6.5	145	On admission.
Oct. 2— 9.30 A. M.	23	15	66	6.1	5.81	4.0	130	Condition worse. 2 hours before delivery by C. S.
Delivered Oct. 2—11.30 A. M.								
Oct. 3— 9.30 A. M.	20	12	61	5.3	5.42	—	130	22 hours p. p.
Oct. 4— 9.15 A. M.	14	7	51	3.4	5.04	3.0	120	46 hours p. p.
Oct. 5— 9.00 A. M.	14	8	54	3.1	5.39	—	120	3 days p. p.
Oct. 6— 9.15 A. M.	14	8	57	2.9	5.99	1.75	115	4 days p. p.
Oct. 13— 9.00 A. M.	17	8	49	2.6	7.54	0.5	110	11 days p. p.

CASE 13.

Chronic nephritis (moderately severe) without convulsions. Hosp. No. 10757. Col. 29. 3 children. 1 miscarriage.

DATE—1920	Total N. P. N. Mg. per 100 c.c.	Urea N. Mg. per 100 c.c.	Urea N. / N. P. N. Per cent	Uric acid Mg. per 100 c.c.	Plasma protein Per cent	Albumin in urine G. per L.	Systolic B. P. MM.	REMARKS
Oct. 14— 9.30 A. M.	19	11	57	2.0	7.31	1.5	240	36 hrs. after admission.
Oct. 18—11.30 A. M.	19	11	55	1.5	7.31	0.25	145	Just before introduction of bougie.
Oct. 19— 9.00 A. M.	19	12	66	1.4	6.84	0.50	155	Early in labor— 22 hours a. p.
Delivered Oct. 20—7.00 A. M.								
Oct. 20—11.00 A. M.	20	14	70	2.2	6.81	0.75	160	4 hours p. p.
Oct. 21— 9.30 A. M.	29	19	65	3.5	7.18	0.50	150	28 hours p. p.
Oct. 22— 9.00 A. M.	24	17	72	2.3	6.91	0.5	145	52 hours p. p.
Oct. 23—10.00 A. M.	27	15	58	1.7	6.63	0.5	155	4 days p. p.

CASE 14.

Pre-eclamptic toxemia (severe), very slow recovery. Hosp. No. 11474. Col. 16. Primigravida.

DATE—1921	Total N. P. N. Mg. per 100 c.c.	Urea N. Mg. per 100 c.c.	Urea N. / N. P. N. Per cent	Uric acid Mg. per 100 c.c.	Plasma protein Per cent	Albumin in urine G. per L.	Systolic B. P. MM.	REMARKS
Nov. 3—12.15 P. M.	19	8	44	2.6	7.39	30.0	160	At venesection.
Nov. 4—10.40 A. M.	26	12	48	2.9	—	4.0	140	Slightly improved.
Nov. 5— 9.30 A. M.	24	15	61	1.3	4.89	4.0	135	
Nov. 6— 9.00 A. M.	25	14	56	3.2	4.99	5.0	145	No change in condition.
Nov. 7— 8.45 A. M.	28	14	50	3.0	5.43	9.0	130	
Nov. 8— 8.40 A. M.	24	14	57	3.0	5.83	20.0	145	Considerably worse.
Delivered Nov. 8—3.00 P. M.								
Nov. 9— 9.30 A. M.	22	14	62	3.0	5.28	10.0	140	18 hours p. p.
Nov. 10—12 Noon	24	13	55	4.8	5.16	8.0	150	45 hours p. p.
Nov. 11— 9.45 A. M.	20	9	45	4.6	5.76	4.0	130	67 hours p. p.
Nov. 12— 9.00 A. M.	19	7	35	3.4	5.54	4.0	130	3 days p. p.
Nov. 14— 8.30 A. M.	17	8	44	2.5	5.61	2.0	125	5 days p. p.

CASE 15.

Chronic nephritis without convulsions. Hosp. Nos. 10771 and 10844. Col. 19. Primigravida.

DATE—1920	Total N. P. N. Mg. per 100 c.c.	Urea N. Mg. per 100 c.c.	Urea N. / N. P. N. Per cent	Uric acid Mg. per 100 c.c.	Plasma protein Per cent	Albumin in urine G. per L.	Systolic B. P. MM.	REMARKS
Oct. 21— 3.00 P. M.	21	—	—	2.6	7.26	—	—	7th month.
Nov. 5— 8.30 P. M.	23	12	52	3.1	6.97	2.0	180	1st admission. At venesection.
Nov. 8—12 Noon	30	20	65	3.5	7.46	—	—	Somewhat improved.
Dec. 12—12.30 P. M.	26	14	53	5.2	—	1.25	205	2nd admission.
Delivered Dec. 15—1.30 A. M.								
Dec. 15—11.30 A. M.	40	25	62	5.8	—	2.0	170	10 hours p. p.
Dec. 17—11.30 A. M.	27	13	47	2.4	—	tr.	160	58 hours p. p.

CASE 16.

Chronic nephritis without convulsions (early, severe). Hosp. No. 10787. White 33. 6 children. 1 miscarriage.

DATE—1920	Total N. P. N. Mg. per 100 c.c.	Urea N. Mg. per 100 c.c.	Urea N. / N. P. N. Per cent	Uric acid Mg. per 100 c.c.	Plasma protein Per cent	Albumin in urine G. per L.	Systolic B. P. MM.	REMARKS
Nov. 10—10.00 A. M.	30	25	83	2.8	7.35	5.0	220	Day after admission.
Delivered Nov. 12—10.00 A. M.								
Nov. 12—12 Noon	76	60	79	9.5	9.09	1.5	185	At close of abdominal hysterotomy.
Nov. 13—12 Noon	76	60	79	6.5	6.14	1.0	200	25 hours after operation.
Nov. 16—12 Noon	96	77	81	10.4	7.77	0.75	165	4 days after operation.
Nov. 22— 9.15 A. M.	38	27	70	6.0	6.92	tr.	165	10 days after operation.

CASE 16.

Whole blood.

DATE—1920	Total N. P. N. Mg. per 100 c.c.	Urea N. Mg. per 100 c.c.	Urea N. / N. P. N. Per cent	Uric acid Mg. per 100 c.c.	Blood protein Per cent	Albumin in urine G. per L.	Systolic B. P. MM.	REMARKS
Nov. 10—10.00 A. M.	37	17	47	2.6	21.14	5.0	220	Day after admission.
Delivered Nov. 12—10.00 A. M.								
Nov. 13—12 Noon	83	60	72	6.6	21.58	1.5	185	25 hours after operation.
Nov. 16—12 Noon	99	71	72	8.8	20.45	0.75	165	4 days after operation.
Nov. 22— 9.15 A. M.	45	23	52	6.3	18.44	tr.	165	10 days after operation.

CASE 17.

Nephritic toxemia without convulsions (early, severe). Hosp. No. 10797. Col. 33. 9 children.

DATE—1920	Total N. P. N. Mg. per 100 c.c.	Urea N. Mg. per 100 c.c.	Urea N. / N. P. N. Per cent	Uric acid Mg. per 100 c.c.	Plasma protein Per cent	Albumin in urine G. per L.	Systolic B. P. MM.	REMARKS
Nov. 17—10.00 A. M	21	12	57	2.3	8.05	0.5	225	Immediately before operation.
Removal of 3 months' fetus, Nov. 17—12 Noon.								
Nov. 20— 9.30 A. M.	26	21	80	4.5	8.62	tr.	155	3 days after abortion.
Nov. 22— 9.30 A. M.	28	22	79	2.9	7.48	tr.	160	5 days after abortion.

CASE 17.

Whole blood.

DATE—1920	Total N. P. N. Mg. per 100 c.c.	Urea N. Mg. per 100 c.c.	Urea N. / N. P. N. Per cent	Uric acid Mg. per 100 c.c.	Blood protein Per cent	Albumin in urine G. per L.	Systolic B. P. MM.	REMARKS
Nov. 17—10.00 A. M.	25	11	42	2.1	19.38	0.5	225	Immediately before operation.
Removal of 3 months' fetus, Nov. 17—12 Noon.								
Nov. 20— 9.30 A. M.	34	18	54	3.3	19.39	tr.	155	3 days after abortion.
Nov. 22— 9.30 A. M.	36	20	55	2.9	17.20	tr.	160	5 days after abortion.

CASE 18.

Ante-partum eclampsia. Hosp. No. 10541. Col. 17. Primigravida.

DATE—1920	Total N. P. N. Mg. per 100 c.c.	Urea N. Mg. per 100 c.c.	Urea N. / N. P. N. Per cent	Uric acid Mg. per 100 c.c.	Plasma protein Per cent	Albumin in urine G. per L.	Systolic B. P. MM.	REMARKS
May 30—11.15 A. M.	22	13	59	5.9	6.41	1.0	170	7 hours after first convulsion.
May 30— 4.15 P. M.	29	17	60	7.5	7.06	—	180	At venesection.
Delivered May 31—3.30 A. M.								
June 2—10.00 A. M.	37	28	75	6.5	5.63	2.0	160	55 hours p. p.
June 3— 9.00 A. M.	32	24	75	3.9	6.28	0.75	140	3 days p. p.
June 9— 9.00 A. M.	26	17	64	3.0	7.53	tr.	120	9 days p. p.
June 22— 9.45 A. M.	24	17	70	2.5	8.08	tr.	125	22 days p. p. on discharge.
1921 Nov. 29— 3.00 P. M.	30	18	60	1.6	7.79	0	130	18 months later.

CASE 19.

Ante-partum eclampsia (mild, prompt recovery). Hosp. No. 10729. White 21. Primigravida.

DATE—1920	Total N. P. N. Mg. per 100 c.c.	Urea N. Mg. per 100 c.c.	Urea N. / N. P. N. Per cent	Uric acid Mg. per 100 c.c.	Plasma protein Per cent	Albumin in urine G. per L.	Systolic B. P. MM.	REMARKS
Oct. 2— 2.30 P. M.	13	6	45	2.9	6.29	0	180	Immediately after first convulsion.
Oct. 3— 9.00 A. M.	15	8	56	4.1	6.44	0.2	130	Improved, no convulsions for 15 hours.
Oct. 4— 9.15 A. M.	16	8	49	6.5	7.10	—	145	In labor—5 hours a. p.
Delivered Oct. 4—2.00 P. M.								
Oct. 5— 9.30 A. M.	19	10	54	6.3	6.50	0.2	150	20 hours p. p.
Oct. 6— 9.30 A. M.	20	11	57	4.2	6.52	—	140	44 hours p. p.
Oct. 7— 9.00 A. M.	20	11	53	3.5	6.49	0.2	120	3 days p. p.
Oct. 16— 9.00 A. M.	24	10	42	2.7	7.36	tr.	110	12 days p. p. on discharge.

CASE 20.

Ante-partum eclampsia (slow recovery). Hosp. No. 11503. Col. 30. 1 miscarriage.

DATE—1921	Total N. P. N. Mg. per 100 c.c.	Urea N. Mg. per 100 c.c.	Urea N. / N. P. N. Per cent	Uric acid Mg. per 100 c.c.	Plasma protein Per cent	Albumin in urine G. per L.	Systolic B. P. MM.	REMARKS
Dec. 1—11.45 A. M.	32	18	57	5.4	5.66	9.0	190	On admission.
Dec. 2— 2.00 P. M.	29	19	65	4.9	5.65	6.0	180	At venesection—after two convulsions.
Dec. 3—10.00 A. M.	39	26	69	7.4	5.29	4.0	165	Improved, no more convulsions. 3 hours a. p.
Delivered Dec. 3—1.20 P. M.								
Dec. 4— 9.45 A. M.	50	30	60	9.9	5.56	2.0	155	20 hours p. p.
Dec. 5— 9.15 A. M.	33	19	57	6.5	5.04	2.0	155	44 hours p. p.
Dec. 9—10.00 A. M.	20	9	48	1.6	6.55	1.5	145	6 days p. p.

CASE 21.

Ante-partum eclampsia (severe, prompt recovery). Hosp. No. 11538. White 17. Primigravida.

DATE—1921	Total N. P. N. Mg. per 100 c.c.	Urea N. Mg. per 100 c.c.	Urea N. / N. P. N. Per cent	Uric acid Mg. per 100 c.c.	Plasma protein Per cent	Albumin in urine G. per L.	Systolic B. P. MM.	REMARKS
Dec. 19—10.45 A. M.	29	14	49	10.9	6.15	1.05	165	2 hours after last convulsion.
Dec. 19— 4.15 P. M.	34	17	50	10.1	5.68	0.50	150	7 hours after last convulsion.
Dec. 20— 9.45 A. M.	37	19	52	10.2	6.08	—	—	In labor, early in second stage.
Delivered Dec. 20—11.30 A. M.								
Dec. 21— 9.30 A. M.	40	23	56	9.2	5.34	1.0	145	22 hrs. p. p. Convalescent.
Dec. 22— 9.15 A. M.	32	15	48	8.3	5.82	0.5	140	46 hours p. p.
Dec. 23—10.00 A. M.	27	12	42	4.8	5.84	0.5	110	3 days p. p.

CASE 21.

Ante-partum eclampsia.

	Whole Blood.				Corpuscles.*			
DATE—1921	Total N. P. N. Mg. per 100 c.c.	Urea N. Mg. per 100 c.c.	Urea N. / N. P. N. Per cent	Uric acid Mg. per 100 c.c.	Total N. P. N. Mg. per 100 c.c.	Urea N. Mg. per 100 c.c.	Urea N. / N. P. N. Per cent	Uric acid Mg. per 100 c.c.
Dec. 19—10.45 A. M.	37	12	33	8.3	52	9	17	4.1
Dec. 19— 4.15 P. M.	38	15	40	9.2	44	12	26	7.6
Dec. 20— 9.45 A. M.	43	16	38	9.2	52	12	23	7.7
Delivered Dec. 20—11.30 A. M.								
Dec. 21— 9.30 A. M.	48	21	43	8.9	62	14	23	8.2
Dec. 22— 9.15 A. M.	41	17	42	7.3	57	21	37	5.9
Dec. 23—10.00 A. M.	34	13	39	3.7	46	17	36	2.5

* Corpuscular values calculated from the hematocrit readings and the determinations on plasma and whole blood.

CASE 22.

Post-partum eclampsia (severe, prompt recovery). Hosp. No. 10578. Col. 22. Primigravida.

Delivered June 16—6.30 A. M.

DATE—1920	Total N. P. N. Mg. per 100 c.c.	Urea N. Mg. per 100 c.c.	Urea N. / N. P. N. Per cent	Uric acid Mg. per 100 c.c.	Plasma protein Per cent	Albumin in urine G. per L.	Systolic B. P. MM.	REMARKS
June 16—11.30 A. M.	52	41	78	8.8	6.38	0	180	After first convulsion. 5 hours p. p.
June 16— 5.00 P. M.	54	43	79	8.7	6.81	ft. tr.	170	At venesection after four convulsions.
June 17— 2.30 P. M.	66	52	79	12.5	6.25	tr.	140	Six hours after last convulsion.
June 18— 7.00 A. M.	57	46	80	9.1	5.77	tr.	140	Convalescent— 48 hours p. p.
June 19— 9.15 A. M.	47	35	74	6.6	6.78	tr.	130	3 days p. p.
June 20—10.00 A. M.	38	25	66	6.2	7.76	tr.	125	4 days p. p.
June 21—10.00 A. M.	31	24	77	7.0	6.85	tr.	115	5 days p. p.
June 23— 9.15 A. M.	29	21	75	3.8	7.06	ft. tr.	110	7 days p. p.

CASE 23.

Nephritic toxemia with convulsions (recovery). Hosp. No. 10769. White 38. Primigravida.

DATE—1920	Total N. P. N. Mg. per 100 c.c.	Urea N. Mg. per 100 c.c.	Urea N. / N. P. N. Per cent	Uric acid Mg. per 100 c.c.	Plasma protein Per cent	Albumin in urine G. per L.	Systolic B. P. MM.	REMARKS
Oct. 21—11.30 A. M.	41	24	58	10.7	6.30	9.0	185	After two convulsions.
Oct. 22— 9.00 A. M.	44	33	75	9.6	5.63	2.0	185	In labor—four hours a. p. No more convulsions.
Delivered Oct. 22—1.20 P. M.								
Oct. 23—10.00 A. M.	45	31	68	12.2	5.40	1.0	185	Much improved. 21 hours p. p.
Oct. 24—10.00 A. M.	45	33	74	7.3	5.76	0.5	185	2 days p. p.
Oct. 25— 9.30 A. M.	—	41	—	8.7	5.71	0.5	180	3 days p. p.
Oct. 26—10.30 A. M.	34	23	68	8.9	6.59	0.25	155	4 days p. p.
Oct. 27— 9.30 A. M.	34	25	75	4.7	6.68	0.25	165	5 days p. p.
Nov. 1—10.30 A. M.	34	22	64	2.5	6.45	tr.	155	10 days p. p.
1921 Nov. 8— 3.00 P. M.	25	15	60	1.2	7.03	tr.	160	1 year after delivery.

CASE 23.

Whole blood.

DATE—1920	Total N. P. N. Mg. per 100 c.c.	Urea N. Mg. per 100 c.c.	Urea N. / N. P. N. Per cent	Uric acid Mg. per 100 c.c.				REMARKS
Oct. 21—11.30 A. M.	46	21	47	9.4				After two convulsions.
Delivered Oct. 22—1.20 P. M.								
Oct. 25— 9.30 A. M.	—	43	—	8.0				3 days p. p.
Oct. 26—10.30 A. M.	41	25	62	7.5				4 days p. p.
Oct. 27— 9.30 A. M.	42	26	62	4.9				5 days p. p.
Nov. 1—10.30 A. M.	44	22	51	4.3				10 days p. p.

CASE 24.

Nephritic toxemia with convulsions (twins, recovery). Hosp. No. 11459. Col. 27. 5 children.

DATE—1921	Total N. P. N. Mg. per 100 c.c.	Urea N. Mg. per 100 c.c.	Urea N. / N. P. N. Per cent	Uric acid Mg. per 100 c.c.	Plasma protein Per cent	Albumin in urine G. per L.	Systolic B. P. MM.	REMARKS
Nov. 13—11.45 A. M.	24	9	36	7.6	7.34	2.0	190	On admission. After six convulsions.
Delivered Nov. 13—12 Midnight.								
Nov. 14—12.30 P. M.	31	19	62	8.1	6.38	tr.	180	12 hours p. p.
Nov. 15— 8.45 A. M.	33	19	57	6.4	7.02	tr.	180	32 hours p. p.
Nov. 16—10.00 A. M.	31	17	55	4.4	6.91	tr.	145	3 days p. p.
Nov. 17—11.00 A. M.	28	15	55	3.3	6.86	None	130	4 days p. p.
Nov. 18— 9.30 A. M.	28	15	56	2.8	6.95	tr.	130	5 days p. p.
Nov. 19—10.00 A. M.	27	14	53	2.3	7.42	ft. tr.	130	6 days p. p.

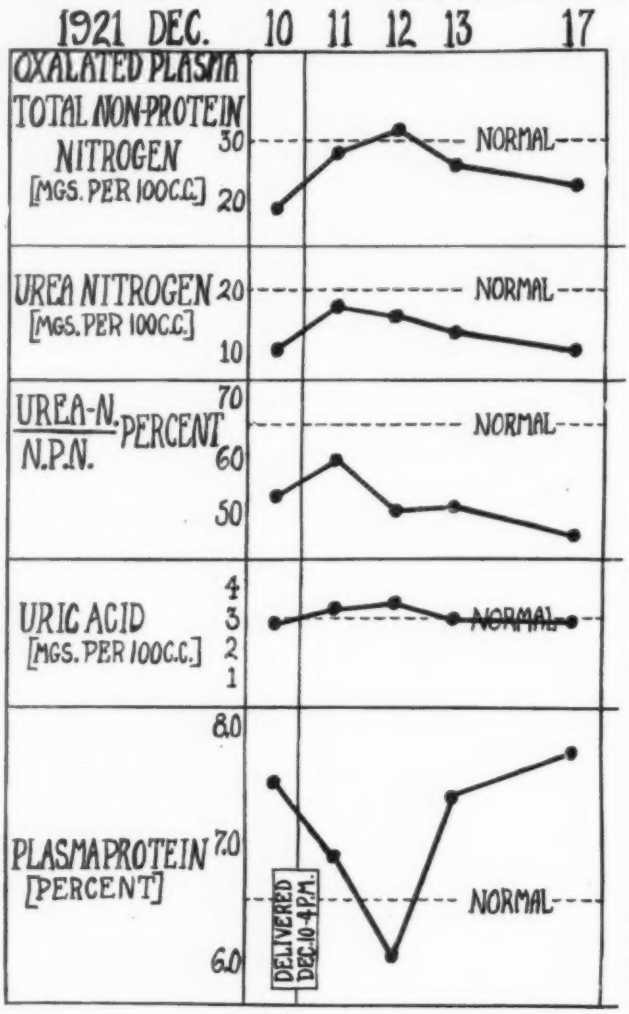

Fig. 1.
Case 7.—Normal primiparous labor.

Toxemia Without Convulsions

The ten cases of late toxemia of pregnancy without convulsions (Nos. 8 to 17) are grouped together because of the uncertainty as to the correctness of the clinical diagnosis. If, however, we apply the usual criteria for differentiation, it would seem that five (Cases 8, 10, 11, 12 and 14) were probably pre-eclamptic in type, whereas the remaining five (Cases 9, 13, 15, 16 and 17) had a definite nephritic basis (nephritic toxemia).

Toxemia with Convulsions

The remaining seven patients had from 2 to 16 general eclamptic convulsions either ante partum (5), intra partum (1), or post partum (1). In the last two cases (Nos. 23 and 24), there were persistent signs of renal insufficiency and a final diagnosis of nephritic toxemia with convulsions was made.

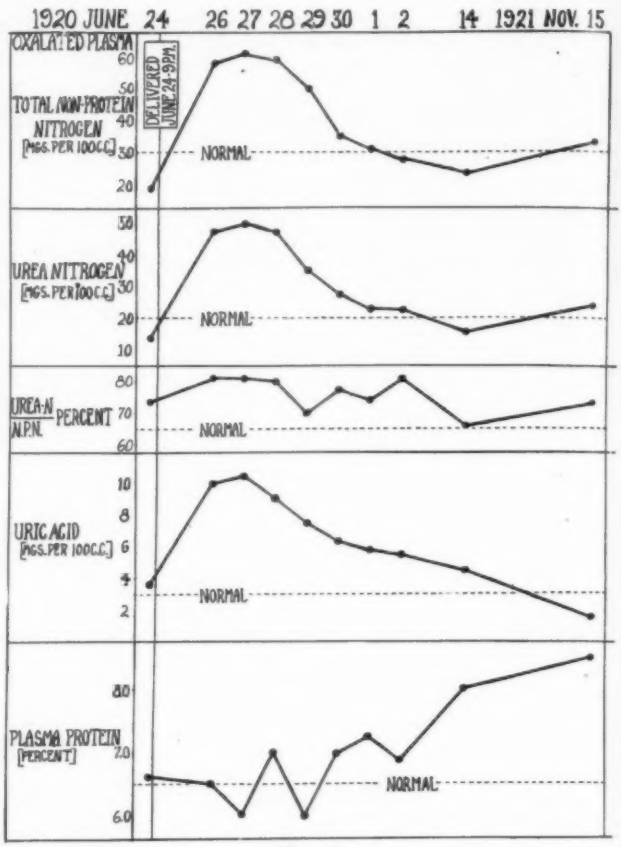

Fig. 2.
Case 9.—Severe nephritic toxemia without convulsions.

Summary of Results

Normal pregnancy.—In the first blood specimens (obtained during labor or immediately after delivery) the non-protein nitrogen and urea nitrogen values fall in the lower range of normal (14 to 23 mg., and 7 to 11 mg. per 100 c.c., respectively), while the Urea N. : N-P.N. ratio is uniformly below 60 per cent. (The patient in Case 2 was not in labor when the operation was performed.) Except in Case 3 the uric acid is also normal. The plasma proteins range around the normal 7.00 per cent.

During the first 48 hours after delivery, there is a tendency for the various non-protein fractions to rise slightly and then fall rapidly to the usual non-pregnant normal range. This is apparent in Cases 1, 3, 4, 5 and 7 for one or all of the constituents studied, while in Cases 2 and 6 it is not evident. Values well within the normal range obtain, however, throughout the period of observation, except that in two instances (Cases 1 and 3) the uric acid is increased after delivery to a point above the generally recognized normal. At the same time, the plasma protein tends to fall (Cases 1, 3, 4, 5, 6 and 7), so that the relative changes in the non-protein constituents

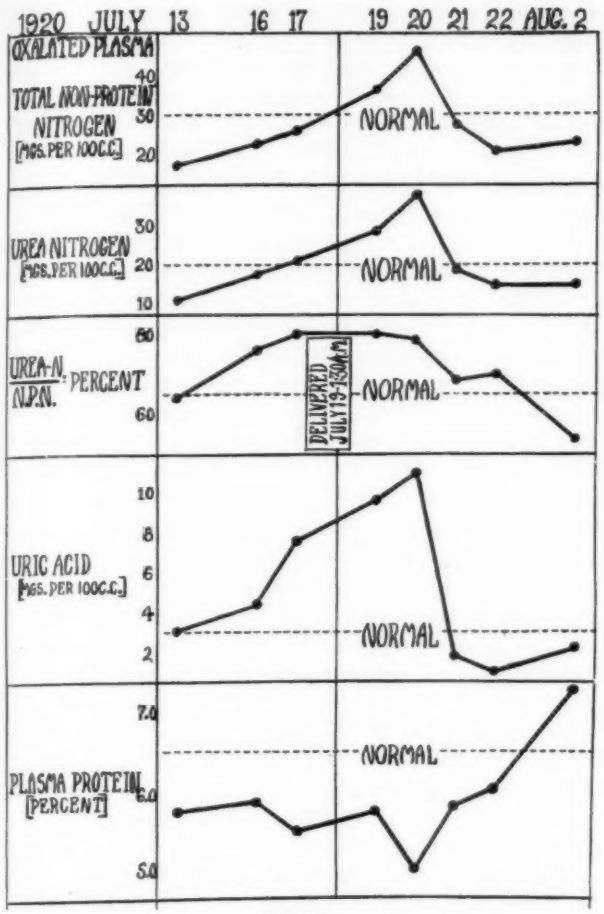

Fig. 3.
Case 10.—Severe pre-eclamptic toxemia.

become more marked. Case 2 is scarcely to be considered as entirely normal, inasmuch as hysterectomy was performed following Cesarian section before the onset of labor.

Toxemia without convulsions.—The first specimens, obtained when the symptoms were most severe, show the non-protein constituents, except the uric acid, to be within the range of normal, and the latter is above 3.5 mgm. in only 3 instances. (Cases 8, 9, and 12.) The plasma proteins vary with the amount of edema, being at or above normal in Cases 13, 14, 15, 16 and 17 and below normal in Cases 8, 9, 10, 11 and 12. The patients were all delivered after varying short intervals of medicinal therapy and the toxic symptoms disappeared with greater or less rapidity. In every instance, some or all of the non-protein fractions have considerably higher values after successful medical treatment (Cases 10 and 15) or after delivery, when the toxic symptoms are disappearing very rapidly. In general, this highest point is attained during the second day following parturition and is associated with an appreciable decrease in the plasma protein percentage.

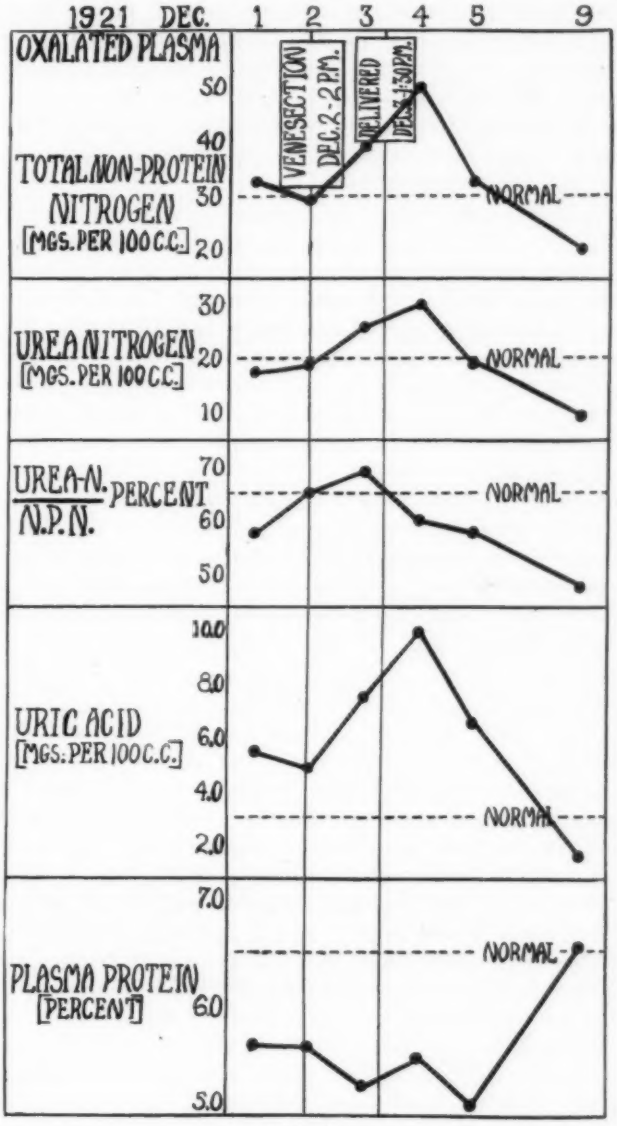

Fig. 4.
Case 20.—Ante-partum eclampsia.

Whole blood determinations were made in Cases 16 and 17 and show the same general variations. In Cases 8 and 14, the post-partum increase is apparent only in the uric acid fraction but in the others it is evident also in the non-protein nitrogen and urea nitrogen. The increase of the urea nitrogen is usually accompanied by an increase of the Urea N. : N-P.N. ratio above the normal of 66 per cent. In general the cases of chronic nephritis, particularly Cases 9 and 16, show the more pronounced variations, but it is doubtful whether any differentiation can be successfully attempted upon such a basis.

Toxemia with convulsions.—In all but two instances (Cases 22 and 23), the total non-protein nitrogen and

urea nitrogen are within the normal range on the first examination, and the Urea N.: N-P.N. ratio is abnormally high only once (Case 22); whereas the uric acid is above normal in all but one instance (Case 10), and here a value of 6.5 mgm. per 100 c.c. is attained before delivery. The plasma protein is generally low, as would be suspected from the extent of the edema.

After clinical improvement, whether induced by delivery (Cases 18 and 24), or by other therapeutic measures (Cases 19, 20, 21, 22 and 23), the various non-protein fractions tend to rise, while the plasma protein decreases. Even though these changes may, in favorable cases, be induced by procedures other than delivery (elimination, venesection and hypnotics), it should be noted that the variations following parturition are more marked. Moreover, if, as usually happens, labor intervenes soon after the convulsions have been controlled by medicinal therapy, the blood changes initiated by this improvement are distinctly accentuated by delivery. In such cases, the high point of the blood non-protein nitrogen may occur during the first 24 hours. In Cases 21 and 23, the parallel whole blood determinations show the same general trend as those of the plasma.

Discussion

The total non-protein nitrogen, urea and uric acid, which may be present in the whole blood or plasma in normal or slightly increased concentrations during the most acute stages of the late toxemias of pregnancy, tend to rise whenever improvement is effected by any of the recognized therapeutic procedures, while at the same time the blood concentration, as judged by the plasma protein content, is considerably lessened. A similar tendency is apparent in supposedly normal women during the early days of the puerperium but the blood changes are never very striking. The extent of these changes in the pathological cases and the rapidity with which normal values are again attained, depend very largely upon the severity of the condition and the rate of clinical improvement. It is also significant that these changes may be detected after either ante-partum or post-partum improvement, as shown by abatement of toxic symptoms, lowering of blood pressure and decreasing albuminuria, but are most marked after delivery. Parturition causes the most pronounced variations, as is to be expected when it is remembered that it is the most effective treatment for all eclamptic conditions. It is equally reasonable to assume that the sudden blood changes are associated with the improvement thus produced rather than with the physiological changes induced by the birth process.

If these alterations had been detected only *post partum* it might have been assumed that they were associated with the increased puerperal excretion of protein decomposition products, which has been studied by Slemons,[13] Longridge [14] and Murlin,[15] but when they are apparent before delivery, they obviously cannot be explained in this fashion. Moreover, the peak of post-partum nitrogen excretion occurs from the third to the sixth day after delivery, whereas the high point of blood nitrogen retention usually appears not later than the second twenty-four hours.

There is, however, a closer association with the increased urinary output (polyuria), which occurs in normal women during the second day of the puerperium (Slemons [13]) and which is generally associated with improvement in women suffering from the various late toxemias. This phenomenon occurs synchronously with a distinct lowering of the plasma protein, a change which is thought to correspond with absorption of the edema fluid. It would seem, then, that there may be some definite relationship between the increase of blood non-protein nitrogen and the resorption of the edema, since both are associated with an increased blood dilution.

Zangemeister [16] has shown statistically, and it is a matter of common experience, that edema is an almost constant accompaniment of late pregnancy. He also considers that this edema is essentially pathological, in that it is the result of some damage to the cells, whereby they become more hydrophilic and imbibe an excess of fluid. In normal pregnancy, these changes are kept within bounds, but when the damage is more extensive, the increased edema initiates a clinical sequence which we recognize as pathological—the late toxemias of pregnancy. The fluid thus attracted to the tissues must be extracted from the plasma and no doubt carries various soluble crystalloid substances with it but has a low protein content. The blood in turn retains more than usual of the ingested fluids, until it becomes more dilute than previously, as indicated by the diminished plasma protein, the lessened depression of the freezing point, and the increased water content. This must probably be looked upon as an attempt to preserve a suitable osmotic pressure relationship between the cell protoplasm and the circulating plasma. There seems to be a rather definite relationship between the extent of the edema and the lowering of the plasma protein concentration, as pointed out by Zangemeister [16] and Rowe,[17] so that in patients with marked general anasarca very low plasma protein values are found. It will be noted in Figure 4 of our next article that the protein curve in toxemic patients is considerably below that observed in normal pregnancy, and that the curves approximate each other only several days after delivery when the edema has been very largely resorbed.

During this process of absorption, which occurs in normal patients very shortly after delivery, and in toxemic individuals during the early stages of improvement, the excess fluid must find its way into the blood stream where it should lead to a still further dilution of the plasma. If this assumption be correct, a definite post-

partum thinning of the plasma should be demonstrable in normal patients, in whom a slight edema is seemingly inevitable, as well as in the toxemic women, in whom edema usually forms a characteristic part of the symptom-complex. That this is generally the case is evident from the tables previously given and from the figures in the next article, in which the developed curves for plasma protein percentage show a decided drop after delivery. This diminished plasma protein concentration is directly associated with the disappearance of the clinical edema, and an increased output of urine.

These findings agree with those of Miller, Keith and Rowntree,[18] who detected an increased plasma volume early in the puerperium of normal women, which they were unable to explain, and with the observations of Stander and Tyler,[19] that, in the period of improvement following eclampsia, the percentage of whole blood and plasma moisture is increased.

Rather little is known about the composition of edema fluid, but if, as is generally accepted on the basis of the injection experiments of Marshall and Davis,[20] the urea is uniformly distributed throughout the body, the excess fluid in the tissues in edema should be in equilibrium with the blood plasma. Resorption of this fluid into the blood might then lead to an increased plasma dilution, particularly if the kidneys were slightly damaged, but should not alter the absolute amounts of urea per unit volume. We have, however, demonstrated that, particularly in markedly edematous patients, the increased dilution of the plasma, which is associated with a decrease in the edema, is accompanied by an increased urea content. It would seem that there are only two possible explanations for these findings; either the edema fluid contains more of these non-protein substances than the plasma, so that the addition of tissue fluid to the blood produces an actual increase in the urea concentration in the plasma, or the kidneys are temporarily affected in such a way as to become partially impermeable to water, so that the plasma dilution increases, and still more impermeable to urea (and the other non-protein nitrogenous constituents of the blood), so that it is retained in greater proportion.

The former, or tissue retention, hypothesis offers a very logical explanation for the observed variations, but has very little support in the way of concrete fact. If, in diseased conditions leading to cellular edema, the tissue-plasma relationship should become so altered that the cell protoplasm could absorb a greater proportion of certain soluble materials along with the water, resorption of the edema should lead to a temporary increase in the plasma concentration of these substances, as well as to a watery dilution of the plasma—changes which we have actually demonstrated. The occurrence of such a tissue retention could be attacked experimentally only by direct analysis of the body tissues, or of the edema fluid, and neither of these procedures was employed. Hammett[21] has offered the only tissue analyses with which we are familiar, when he reported the urea content of a series of placentas from normal and toxemic women. In the latter, the urea concentration is on the average very considerably higher than in the former. He did not attempt simultaneous blood analyses, but in view of the general finding that in such cases the blood urea is either not increased at all, or very slightly, his work may perhaps lend slight support to the hypothesis.

Likewise, there are no available figures on the composition of the edema fluid in eclamptic women, but Strisower[22] has recently reported some observations in nephritic and cardiac patients, which show quite conclusively that at times this fluid may actually contain more non-protein nitrogen than does the whole blood drawn simultaneously. It is interesting that this relation was found to obtain particularly when the kidney parenchyma had been most damaged, and in patients with only renal congestion, conditions that are met in the late toxemias of pregnancy, in which the renal lesions are usually parenchymatous in location and frequently consist of no more than a cloudy swelling.

On the other hand, it must be admitted that, in all cases of toxemic pregnancy and in many normal women following delivery, there is evidence of renal impairment —albuminuria and cylindruria—and that the degree of kidney insufficiency apparently plays a large rôle in determining how great the improvement rise in the blood nitrogen shall be. Thus, in presumably normal women, the post-partum increase, while usually apparent, is always slight, and in mild pre-eclamptic conditions, with very little apparent kidney damage, the evidence of retention is never great, whereas we have observed the most marked evidences of convalescent retention in patients with severe chronic nephritis (Cases 9 and 16). It would appear, then, that the tendency toward higher blood nitrogen values is shown during the stage of improvement by all patients with clinical edema, but that the extent of this rise is determined largely by the degree of renal insufficiency.

However, in certain instances in which improvement preceded delivery (Cases 10, 14, 15, 19, 20, 21 and 23), the clinical change was accompanied by increased evidence of renal insufficiency, as judged by the plasma non-protein nitrogen values, while clinically the kidney function was improved, as indicated by an increased urinary output and a diminishing albuminuria. Moreover, in certain other patients (Cases 12, 13, 14 and 18), in whom the clinical symptoms became more severe under observation, the blood nitrogen rarely increased and in fact occasionally showed a slight drop.

Another observation, which quite certainly involves the question of kidney function, is that the uric acid tends to rise more than the other non-protein fractions. This is evident in two of the so-called normal patients,

in whom the uric acid alone showed a post-partum rise, while in the abnormal cases the uric acid increase is generally proportionately greater than that of the other constituents that have been studied. This is in accord with the usual experience that the kidneys excrete uric acid with considerable difficulty and that even slight derangement of their function may lead to abnormally high concentrations in the blood (Myers, Fine and Lough [23]).

It is thus apparent that there are certain facts which cannot be satisfactorily explained on the basis of renal inefficiency, and it is for this reason that the possibility of tissue retention is considered. For example, in Case 20, the patient became distinctly worse between the time of the collection of the first and second blood specimens, an interval of 26 hours, and yet there was no increase in the blood nitrogen but rather a decrease, while in the next twenty hours (Specimen 3) there was marked clinical improvement associated with a definite rise in all the non-protein constituents and a drop in the plasma protein percentage, in spite of the fact that the patient was in labor. Twenty-four hours later, when the toxic symptoms had largely disappeared and the urinary excretion was much improved, still higher values were obtained. The same tendency toward disagreement between the clinical picture and the blood nitrogen retention is apparent in several other cases and would undoubtedly be more striking many times if the specimens had been collected at different intervals. The changes are so rapid that only occasionally is one fortunate enough to obtain evidence of the maximal alterations. In the patients with severe chronic nephritis, it would appear that both factors, renal impermeability and resorption of an edema fluid with high non-protein content, must unite to furnish evidence of the marked and considerably delayed blood nitrogen retention shown in Cases 9 and 16.

Summary

Repeated examinations of certain non-protein nitrogen fractions and of the protein of the blood plasma have indicated that after delivery in normal patients there is a tendency for the former to rise and for the latter to fall; whereas in patients suffering from the late toxemias of pregnancy these changes are almost invariably accentuated, their extent being determined largely by the severity of the disease. In the latter group, similar but slighter changes can follow medicinal treatment without delivery, a fact which is taken to mean that physiological puerperal alterations cannot be held responsible for the changes, although they may augment the variations appearing when improvement is induced by delivery. By exclusion, a tissue-retention process is suggested as explaining the changes noted, although the effect of renal insufficiency is not to be disregarded. It is appreciated that no particularly pertinent facts are advanced to support the contention, but such a hypothesis seems the only means of explaining the experimental findings.

Conclusions

The period of immediate convalescence from the late toxemias of pregnancy is usually associated with higher plasma non-protein nitrogen values than is the period of the most acute clinical signs. This blood nitrogen rise is synchronous with a fall in the plasma protein percentage, which indicates a plasma dilution. These variations may be noted after improvement induced by any therapeutic procedure, but are most marked after delivery.

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PLASMA PROTEIN VARIATIONS IN NORMAL AND TOXEMIC PREGNANCIES*

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The existence of a blood dilution—hydremia,—and of a concomitant thinning of the plasma—hydroplasmia, during pregnancy has been established by many investigators, who have attacked the problem from various angles. In spite of these proven differences in dilution of the blood and plasma at different periods in the reproductive process, little attention has been paid to the development of a curve, which would indicate the changes to be expected during these periods. It seemed desirable, therefore, to accumulate data along these lines, and the present study was begun with the idea of gathering information concerning the course of these relative changes in plasma dilution in both normal and toxic pregnancies. It was further believed that such changes could be interpreted as representing the direction, though probably not the true extent, of variations in the volume of the circulating plasma and thereby logically of the whole blood, since the fluid part of the blood is much more susceptible to volume changes than are its formed elements.

From the various procedures available for such a relative study, determination of the total plasma proteins was decided upon as offering the most accurate and rapid information. These substances are of a colloid nature and consequently do not pass freely, if at all, through the blood vessel walls, so that rapid changes in dilution of the blood are evidenced by significant variations in their concentration. Moreover, there is available in the Kjeldahl procedure a method of established accuracy, which can be employed to great advantage. Some hundreds of specimens of plasma were thus studied and the results obtained form the basis of this communication.

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HISTORICAL

Without mentioning the numerous investigators who have demonstrated an increased whole blood dilution during normal pregnancy, it may be pointed out that a true hydroplasmia has been shown by

(1) a lower specific gravity, (Nasse,[1] and Zangemeister [2]),

(2) an increased water content and diminished total solids, (Zangemeister,[2] Stander and Tyler,[3] and de Wesselow [4]),

(3) a diminished freezing point depression, (Zangemeister [2]),

(4) a diminution of the plasma or serum proteins, (Zangemeister,[2] Eckelt,[5] Landsberg,[6] Dienst,[7] and Fahraeus [8]).

Moreover, by the dye injection method, Miller, Keith and Rowntree [9] have shown an actual increase in the quantity of circulating plasma per unit of body weight.

These published results likewise give some indication as to the form which the curve of plasma dilution takes, although the complete picture has never been developed. For example, de Wesselow [4] says: "Lastly, the estimations of the total solids of serum strongly suggest a progressive dilution of the blood during pregnancy, the percentage of water increasing with the length of gestation." Stander and Tyler [3] found that "After the first month, which may be attended with a low plasma moisture, the water increases gradually to the fifth month, after which it falls slowly until the time of labor." Zangemeister,[10] Dienst,[7] Eckelt,[5] and Landsberg,[6] who have worked extensively on plasma proteins during pregnancy, agree that there is a decrease during gestation, and particularly in the last four months, with an increase at the time of labor, but from none of their reports is it possible to construct a complete picture.

Changes in plasma dilution occurring during the normal puerperium have been largely ignored, so that it is impossible from previous work to gain any adequate conception of the daily changes which lead, in the course of seven to ten days, to the re-establishment of normal non-pregnant conditions. Miller, Keith and Rowntree [9] postulated a decreased plasma volume in the puerperium as a result of their studies with the injection of vital red, but noted in several cases that "there

was relatively little decrease or even an increase in the blood volume after labor." An examination of their protocols shows that these determinations were made during the first four days of the puerperium, and that, when two of these patients were studied again a few days later, the expected decrease in plasma volume was found. In the same place they say: "These studies indicate that there is an increase in the absolute and relative values of both plasma and blood late in pregnancy with a slow return to normal during the puerperium."

De Wesselow's [4] figures for total solids in the serum would indicate that during the period from three to eleven days *post partum* there is still a considerable dilution, which has, however, entirely disappeared at the end of seven weeks. Dienst [7] and Zangemeister [2] report a few values for the plasma proteins during the puerperium but fail to say at what period after delivery the specimens were obtained, while Eckelt [5] found the plasma protein at normal non-pregnant figures in the puerperium but does not indicate the interval *post partum*.

Most of the evidence available regarding possible changes in plasma dilution during the late toxemias of pregnancy is contained in the reports of Eckelt,[5] Dienst [7] and Zangemeister,[11] although Stander and Tyler [3] state that the plasma moisture is increased in these patients. Zangemeister [11] has particularly stressed the diminution of the plasma protein occurring in these conditions and upon the basis of his findings has elaborated a theory concerning their etiology—the hydrops gravidarum hypothesis. These investigators have shown that, in eclampsia as well as in the other pregnancy toxemias not associated with convulsions, there is usually a further diminution of the plasma proteins to a point below that obtaining in normal gestation. Moreover, it is insisted that this decrease is roughly proportional to the amount of tissue edema. Rowe [12] has also stressed this relationship in patients suffering from chronic nephritis.

Neither Zangemeister [11] nor Dienst [7] refer particularly to the changes in plasma dilution which occur during convalescence from eclampsia, but Eckelt,[5] who found low values in the pregnancy toxemias, noted that they remained low during the early polyuria and then rapidly rose to normal. Rowe [12] says that in chronic nephritis the plasma protein values return to normal as the edema disappears, and from Javal's [13] protocols it is evident that he noted the same thing in his eclamptic patients. Stander and Tyler [3] state that in the period of improvement following eclampsia the percentage of whole blood and plasma moisture is increased.

Dienst [7] studied two patients with hyperemesis gravidarum and found normal serum protein values.

Experimental

The blood samples were collected in tubes containing sufficient powdered potassium oxalate to prevent clotting, and were then centrifuged so that the clear plasma could be obtained by siphoning. Ordinarily, the determinations were begun within an hour, but occasionally the bloods were preserved over night in the ice-chest. The analyses were made on 1 c.c. portions of the plasma by the marco-Kjeldahl method, copper sulphate, potassium sulphate and sulphuric acid being employed. Upon distillation the ammonia was collected in N/14 H_2SO_4, and alizarin was generally employed for the back titration. All analyses were done in duplicate and a third sample was reserved to be run later if the duplicates failed to agree. Agreement to within three per cent was insisted upon. In all the pathological samples and in the majority of the normals, the total non-protein nitrogen was determined by the Folin-Wu [14] procedure, while in the others an arbitrary value (25 mg. per 100 c.c.) was subtracted from the total nitrogen to give the protein nitrogen. This figure was then multiplied by the constant 6.25 to obtain the percentage of plasma protein. Hematocrit values were obtained by centrifuging the oxalated blood at high speed for 20 minutes.

In no instance was an individual followed through pregnancy and the puerperium, but several patients were examined frequently during the post-partum period, and the average and the individual curves showed a close agreement.

The results obtained are shown in the following tables and are graphically represented in the corresponding charts, in which the dots represent separate specimens and the lines indicate the averages.

TABLE I.

Plasma protein variations in normal pregnancy.

Diagnosis		No. of patients	Plasma protein percentage	
			Range	Average
Non-pregnant		22	6.45—7.83	7.04
Pregnant	1-2 mos.	9	6.29—7.78	6.93
	3 mos.	12	6.22—7.14	6.63
	4 mos.	7	6.13—6.81	6.51
	5 mos.	7	5.81—6.89	6.33
	6 mos.	10	5.70—6.81	6.21
	7 mos.	11	5.70—7.08	6.27
	8 mos.	10	5.86—7.04	6.38
	9 mos.	10	5.78—7.31	6.46
	10 mos.	12	5.80—7.67	6.61
Parturient		9	5.36—7.56	6.85
Puerperal	1 day	6	6.33—7.61	6.90
	2 days	6	5.87—7.23	6.48
	3 days	6	5.96—7.39	6.52
	4 days	6	5.83—7.23	6.50
	5 days	5	6.25—6.80	6.46
	6 days	4	6.33—7.43	6.84
	7 days	4	6.28—7.94	7.09
	2 wks.	12	6.29—7.07	6.77
	3 wks.	7	6.53—7.69	6.98

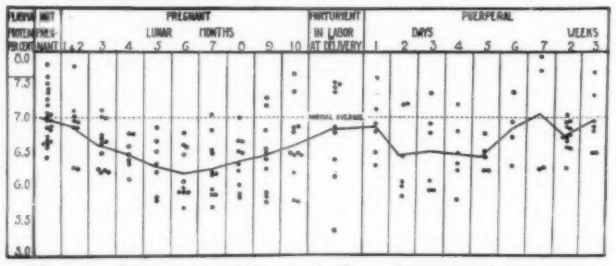

Fig. 1.—Plasma protein variations in normal pregnancy, labor and puerperium.

TABLE II.

Plasma protein variations in patients with the late toxemias of pregnancy without convulsions.

DIAGNOSIS		No. of patients	Plasma protein percentage	
			Range	Average
Pregnant	9 mos.	9	4.87—6.63	5.62
	10 mos.	6	5.57—6.46	5.91
Parturient		3	5.48—7.04	6.45
Puerperal	1 day	5	5.38—6.81	5.91
	2 days	8	4.99—7.18	5.92
	3 days	7	5.39—6.91	6.04
	4 days	7	5.54—7.14	6.41
	5 days	2	6.08—7.64	6.86
	6 days	2	5.61—6.98	6.29
	7 days	1	7.30	7.30
	2 wks.	4	6.82—7.68	7.39
	3 wks.	3	7.53—8.01	7.71

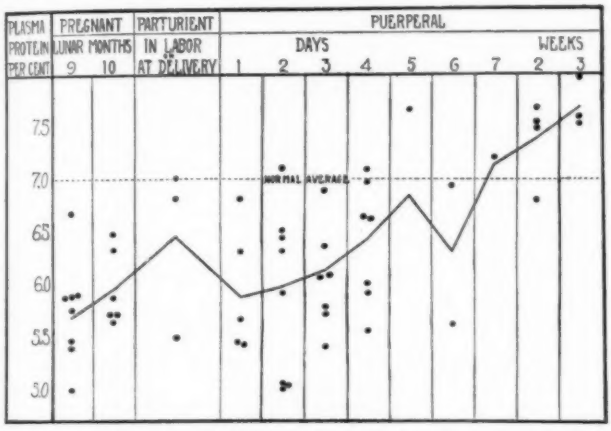

Fig. 2.—Plasma proteins in the late toxemias of pregnancy without convulsions.

TABLE III.

Plasma protein variations in patients with the late toxemias of pregnancy with convulsions.

DIAGNOSIS		No. of patients	Plasma protein percentage	
			Range	Average
Pregnant	9 mos.	4	5.71—6.44	6.12
	10 mos.	5	5.65—6.41	6.04
Parturient		5	5.29—7.34	6.29
Puerperal	1 day	8	5.34—6.81	6.04
	2 days	6	5.04—7.02	6.07
	3 days	6	5.63—6.91	6.06
	4 days	5	6.28—6.86	6.60
	5 days	3	6.68—7.76	7.13
	6 days	3	6.55—7.42	6.94
	7 days	—	— —	—
	2 wks.	6	6.45—7.53	6.97
	3 wks.	2	6.13—7.34	6.73

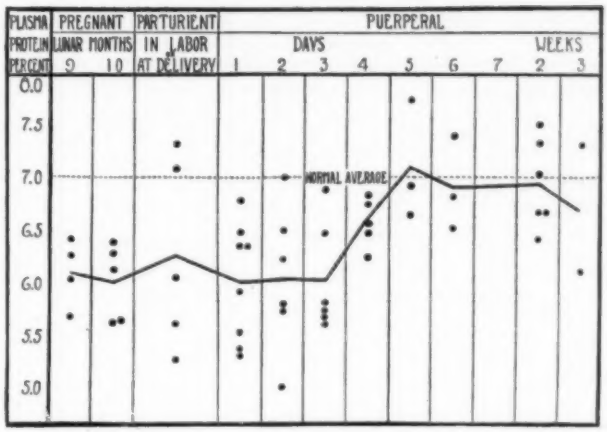

Fig. 3.—Plasma proteins in the late toxemias of pregnancy with convulsions.

Serum shows values similar to, but slightly lower than, those obtaining for plasma, probably by reason of the absence of fibrin in the former. Thus, in the tenth lunar month of pregnancy the following values were found:—

	Serum protein percentage		
	No. of patients	Range	Average
Normal pregnancy	7	5.65—7.49	6.43
Toxemia without convulsions..	7	4.51—5.81	5.17
Toxemia with convulsions.....	6	5.03—6.36	5.77

A few plasma protein determinations were done upon the blood of women suffering from the severe vomiting of early pregnancy, and it was found that the values were generally higher than usual, depending upon the degree of dehydration, but returned rapidly to the early pregnancy normal, as soon as fluids could be retained. In a typical case, the consecutive values were:

Date 1923	Plasma protein percentage	Condition and diet
Nov. 24	7.29	Admitted with persistent vomiting
Nov. 26	7.04	Fluids by rectum
Nov. 28	7.56	Solids by mouth
Nov. 30	6.48	Ordinary diet

Hematocrit readings were obtained upon a great many of the specimens from normal individuals and the results are summarized in the following table:

TABLE IV.
Hematocrit readings in normal pregnancy, showing plasma volume percentage.

DIAGNOSIS		No. of patients	Plasma volume percentage	
			Range	Average
Normal Non-pregnant		14	54.4—65.2	60.5
Pregnant	0- 8 wks.	7	57.1—68.0	63.6
	8-12 wks.	11	60.9—69.1	64.6
	12-16 wks.	6	61.1—68.8	65.1
	16-20 wks.	7	65.9—72.8	69.4
	20-24 wks.	9	63.9—72.9	67.9
	24-28 wks.	10	64.9—71.7	67.6
	28-32 wks.	10	61.0—70.4	67.8
	32-36 wks.	8	66.3—72.3	69.4
	36-40 wks.	10	63.4—72.0	68.4
Parturient		3	60.3—64.7	62.5
Puerperal	1st wk.	7	63.4—73.9	69.6
	2nd wk.	11	62.3—68.3	65.9
	3rd wk.	5	62.8—69.6	65.3

Comparison of these values with those in Table I shows that, as the plasma protein percentage decreases, the plasma volume percentage of the whole blood rises. This divergence is well shown in Figure 4, in which the two sets of averages are plotted against each other. It should be noted that the maximum increase in plasma volume percentage occurs during the sixth month of normal pregnancy, when the plasma proteins are at their lowest point.

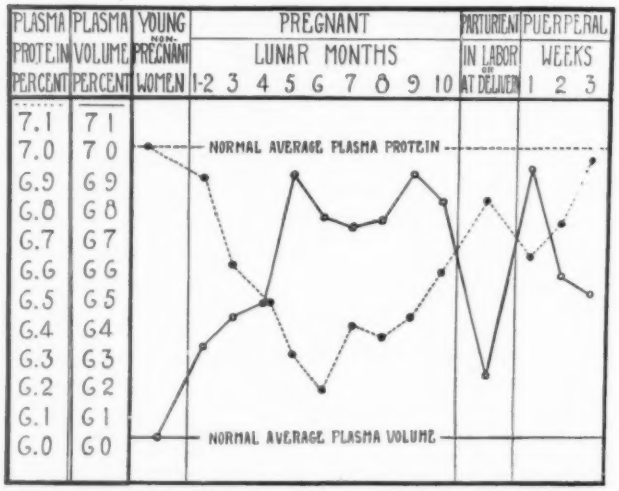

Fig. 4.—Plasma volume and plasma protein in normal pregnant women.

Summary of Results.—In twenty-two healthy, non-pregnant women in the child-bearing age the plasma proteins varied from 6.45 to 7.83 per cent with an average of 7.04 per cent (Figure 1).

During normal pregnancy, the plasma proteins begin to fall during the third lunar month, or occasionally even before that period, and decrease gradually to a minimum at the sixth month, after which there is a slow rise during the latter months of pregnancy with the values at the tenth month still somewhat below normal. A further sharp rise occurs at the time of labor and is continued into the first day *post partum*, but in the next twenty-four hours the proteins suffer an abrupt decrease, which is maintained for three or four days and is followed by a rapid rise to normal at the end of the first week (Fig. 1).

The late toxemias of pregnancy usually develop only during the last months of pregnancy and consequently no significant figures are available for these groups earlier than the ninth lunar month. During the last two months of gestation in these individuals, the average plasma protein values are considerably lower than in normal pregnant women at the same periods, but the form of the developed curve is quite similar to that observed in normal gestation, with a sharp rise during labor, a fall in the early post-partum period, and a subsequent permanent rise to normal (Figs. 2, 3). Upon comparing the three curves, this correspondence can be more easily made out (Fig. 5). It is interesting, and probably of some significance, that in the toxemias without convulsions the average values are at a lower level than in the convulsive group.

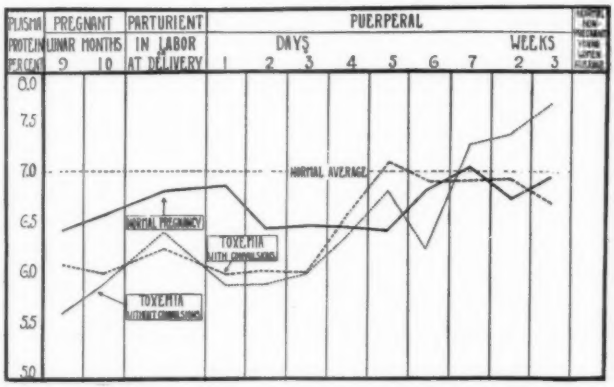

Fig. 5.—Plasma protein; comparing normal pregnancy with the late toxemias.

General Discussion

The facts advanced in the previous section are sufficiently definite to be significant, but their interpretation and explanation are not clear. We believe that the demonstrated decrease in the plasma proteins is the result of a real watery dilution of the blood, and find confirmation for this opinion in the fact that Stander and Tyler [3] found the plasma and blood moisture definitely increased in the fifth, sixth and seventh lunar months of pregnancy, and developed a curve, which is practically the reverse of that

in Figure 1. Moreover, Nasse,[1] and Thompson [15] have shown that the specific gravity of the blood or plasma is lowest at that period.

According to the more modern bio-colloid conception of the blood as a physico-chemical system, water cannot exist in the plasma as such but must be in loose combination with the hydrophilic colloids there present. These water-holding substances are chiefly the proteins, whose swelling ranges are individually different, so that variations in the protein partition of the plasma may lead to changes in its water capacity. Moreover, the hydrophilic properties of these proteins may be influenced by changes in the salt concentration or in the reaction of the medium. There are no available facts from which one can venture to say which of the various possible factors is concerned, although we do know that several of them are altered during pregnancy: the hydrogen-ion concentration is diminished (Hasselbalch and Gammeltoft [16]), the calcium is decreased (Plass and Bogert [17]), and the fibrinogen and albumin are increased at the expense of the globulin fraction (Dienst [7]). All of these changes would tend to increase the water-carrying capacity of the blood and thus lead inevitably to its dilution, but only in the case of calcium have we any evidence that the changes parallel those of the plasma proteins. The curve which we have recently published [17] for serum calcium during pregnancy in general follows the same course as that here presented for normal gestation. Variations in the protein partition are now being studied and may throw further light upon the question.

Whatever may prove to be the fundamental cause of this blood dilution, it would seem from the form of our curve that normally, as pregnancy advances, the body contrives in some way to protect itself from too radical changes so that the blood dilution gradually becomes less marked, until it is only half as great at term as at six months. It is interesting that there is usually no appreciable tissue swelling at the time when the pregnancy dilution is most marked, whereas edema becomes increasingly common as the plasma dilution decreases in the latter months of gestation. On the other hand, the level of the plasma proteins late in pregnancy seems to be definitely associated with the extent of the clinical edema, and is especially low in toxemic women with general anasarca. Probably, the unknown factor that leads to an increased water content in the body of pregnant women, and usually to definite edematous swelling in the last part of the gestation period, will be found to be identical with that producing the plasma dilution, and the relationship between the two will be something more than empirical, although at present we are unable to say what it may be.

The rapid plasma concentration during labor is equally difficult to explain but is probably directly associated with the general tissue change, which also leads to a sudden loss of weight immediately before labor (Zangemeister [18] and Kemper [19]), and to an ante-partum polyuria (Slemons [20]). It is true that during parturition the fluid intake is usually diminished and the perspiration increased, but that these factors are responsible for the relative anhydremia is very doubtful, since the concentration of the blood becomes evident very early in the birth process, and probably even before the onset of labor pains.

Following delivery, the organism rapidly returns to normal when the factors which had served to alter the maternal metabolism during pregnancy suddenly disappear. Among the changes that are so much in evidence in both normal and toxemic individuals, there is none more striking than the return of the body cells to their normal affinity for water. This rapid recovery is associated with a pronounced polyuria beginning on the first or second day (Slemons [20]), and a disappearance of the imperceptible or clinical edema, which seems a part of every pregnancy. This abnormal tissue fluid is suddenly released from the cells, passed into the blood stream and eliminated by the kidneys as rapidly as possible. Under such circumstances, the plasma should become more dilute for a time and then gradually return to normal as the non-pregnant water balance is restored. Our curve (Fig. 1) for normal puerperal women shows such a plasma dilution occurring suddenly on the second day and maintaining itself for three or four days, after which it rapidly disappears. In toxemic patients the same dilution is apparent, but it frequently appears somewhat earlier and is more pronounced. These observations are in accord with those of Miller, Keith and Rowntree [9] that early in the puerperium the plasma volume may equal that observed in late pregnancy, and is considerably greater than that found at the end of a week.

The late toxemias of pregnancy seem to represent merely an exaggeration of some change which is a part of normal pregnancy but which for some reason has not been kept within physiological bounds. The observed changes should then be similar but more pronounced, and it will be seen from Figures 2 and 3 that this is true as regards the plasma protein variations. Both charts show an exaggeration of the normal changes, with the plasma proteins at a lower level than in normal pregnancy, but with the labor rise and subsequent puerperal fall still apparent, the latter appearing somewhat earlier than in normal subjects. The greater ability of the blood of these patients to absorb water is associated with a further increase of hydrogen-ion concentration and of fibrinogen, even though no significant variations in the electrolytes have been demonstrated, the calcium, for example, not being appreciably lower than in normal pregnancy.

In general, the patients who had eclamptic convulsions showed less marked variations than those in whom the toxemia was of the non-convulsive type. Moreover, the extent of the plasma dilution was directly associated with the amount of edema, a fact which has previously been

noted in eclamptic women by Zangemeister,[10] Dienst,[7] and others, and in chronic nephritics by Rowe.[12] The lower values obtaining generally in patients without convulsions can be correlated with the clinical fact that toxic women with little or no edema are more apt to have convulsions than those with marked swelling.

The puerperal changes observed in these patients are comparable to those seen in normal women, but are on an exaggerated scale, so that the post-partum decrease in plasma proteins comes earlier and is more marked. Eckelt[5] also noted these puerperal changes in the serum protein in eclamptic patients and related them to the disappearing edema and consequent polyuria. According to his figures, the lowest point was usually reached on the first or second day, but was occasionally postponed until the third day *post partum*. We, too, believe that this greater plasma dilution is associated with the more pronounced polyuria inaugurated by delivery in edematous women. Normal values are attained at about the same period after delivery as in the normal patients.

By referring to the preceding paper, it is obvious that the greatest plasma dilution occurs in the patients with marked edema (Cases 8, 9, 10, 14, 18, 20, 22 and 23) where with improvement a decided polyuria is to be expected. Moreover, when ante-partum improvement is obtained by measures other than delivery (Cases 10, 14, 20, 21 and 23) the plasma protein values tend to rise as the edema disappears.

This definite association of lowered plasma protein with clinical edema in the pathological cases certainly suggests that the relationship is something more than incidental, and that even in normal pregnancy the plasma dilution must be looked upon as evidence of a sub-clinical edema (in the earlier months), or of a generalized process (in the last months).

The other question as to whether changes in plasma protein concentration can be translated directly into terms of relative plasma volume alterations is also rather difficult, but may probably be answered in the negative, although there is good reason to believe that they indicate the direction if not the extent of such variations.

The colloidal nature of the plasma proteins undoubtedly prevents their free passage out of, or into, the closed circulatory system, although the investigations of Scott,[21] and of Turner, Marshall and Lamson[22] indicate that under certain conditions (severe hemorrhage) the fluid poured into the blood from the tissue spaces may contain an appreciable percentage of protein. It may be assumed that, under reverse conditions, the protein passes in the opposite direction, since recovery from hemorrhage does not lead to an excessive plasma protein content. In all probability, a similar but smaller change occurs under the less extreme conditions encountered in physiological variations of blood volume, such as are met with during gestation.

It is well substantiated that during pregnancy the plasma proteins are diminished (Dienst, Zangemeister, Fahraeus *et al.*), and that the plasma volume is increased (Miller, Keith and Rowntree). Mahnert,[23] who has recently determined the serum protein in pregnant women before and after the intravenous injection of a measured quantity of physiological saline solution (de Crinis' method), and by the observed differences has calculated the total circulating plasma, agrees that there is an increased plasma volume during pregnancy, and especially during the last two months, which is associated with a decrease in the percentage of serum protein, but with an actual increase in its total amount. The experimental results of Miller, Keith and Rowntree,[9] using a dye injection method for plasma volume determinations, serve to confirm Mahnert's work, since they calculated that the plasma volume in the tenth lunar month of pregnancy was approximately 18 per cent greater than in normal men or in women ten days after delivery, whereas our maximum protein decrease amounted to only 10 per cent and was considerably less than that in the last month of gestation.

Stander and Tyler,[3] and de Wesselow,[4] found that the total solids of the plasma suffered a maximum drop of 8 or 9 per cent during pregnancy, figures which agree well with those we have observed, but since the proteins constitute the greater part of the plasma solids, such an agreement was to be expected.

It should, however, be remembered that the dye used by Miller, Keith and Rowntree, and the salt solution employed by Mahnert are known to disappear rapidly from the circulating blood and that errors attributable to such a phenomenon would distort their calculations so that the computed total plasma volume would be somewhat greater than actually existed during the experiment. Moreover, Scott[24] has shown that dilution of the blood with salt solution causes an appreciable increase in the plasma proteins, the addition coming quickly from the corpuscles, a fact which tends to cast some slight doubt upon Mahnert's conclusions. In spite of these objections, it would seem most probable that, while plasma protein variations undoubtedly indicate the direction of plasma volume variations they do not show the true extent of the changes involved.

We, therefore, believe that the curves that we have plotted show the general character of the plasma volume changes occurring during pregnancy, labor and the puerperium in normal and toxic pregnant women. And, indirectly, they must also indicate the relative changes in whole blood volume, since the latter are largely dependent upon plasma volume variations.

Our results, likewise, are capable of some interesting correlations with earlier observations upon the blood changes occurring during pregnancy. Thompson[15] established a curve for the whole blood specific gravity, which shows a low point during the sixth month followed by a

gradual rise to normal at delivery, while the red blood cells and hemoglobin behave very similarly. Williams [25] followed the variations in the whole blood urea and non-protein nitrogen during pregnancy and found them lowest during the fourth to seventh months. Moreover, we [17] have recently published a long series of serum calcium determinations in the form of a curve, the similarity of which to that here presented for normal women (Fig. 1) is quite striking. The maximum drop in the serum calcium appeared at the sixth month of pregnancy and amounted to roughly ten per cent. It was then suggested, in view of this work, that dilution probably played a considerable rôle in the detected changes, and it was insisted that this factor should be considered whenever variations are detected in the blood of pregnant women.

SUMMARY

By plotting the averages of numerous plasma protein determinations upon the blood of normal and toxemic women in all stages of the reproductive cycle, we have developed the approximate curves of plasma dilution in these various conditions. It is believed that these figures show roughly the relative changes of plasma and blood volume occurring normally and pathologically among pregnant women, although the percentage variation is somewhat smaller than that reported by other authors using different methods. No definite explanation for the changes is attempted, but it is suggested that the presence of an appreciable or imperceptible edema may possibly explain the observed physiological and pathological alterations. In the definitely pathological women with the late toxemias of pregnancy, the degree of plasma dilution varies with the amount of clinical edema, and is apt to be less marked in the patients who develop general convulsions, than in those who do not. This finding suggests that edema may be a protective mechanism designed to guard the organism against some general cellular poison developed under certain conditions during gestation.

CONCLUSIONS

The plasma proteins tend to decrease during the early part of pregnancy, reaching a minimum at the sixth month. They then increase somewhat during the latter months, undergo a sharp rise during labor, only to drop precipitately early in the puerperium, and finally rise slowly to normal at the end of the first week *post partum*. In general, patients suffering from the late toxemias of pregnancy have similar variations but the dilution is more marked, depending largely upon the extent of the clinical edema.

The existence of blood and plasma dilution should be considered whenever blood studies are done during pregnancy and labor, or the convalescence therefrom.

We desire to express our thanks to the various helpers who have assisted in this work by obtaining blood samples, and especially to Dr. Walter E. Welz of Detroit who placed at our disposal a large number of patients in the City Pre-natal Clinic. Miss Kathleen McCaw very kindly made the charts.

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PULMONARY INFECTION WITH THE SPIROCHAETAE AND FUSIFORM BACILLI OF VINCENT*

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It is the purpose of this paper to describe briefly a case of pulmonary infection with the spirochaetae and fusiform bacilli of Vincent, a disease closely analogous to pulmonary tuberculosis and, so far as we are able to find, not previously described in the literature. Twelve cases of bronchitis due to these organisms have been described in this country [1,2] and abroad,[3] but none of them had physical signs of definite pulmonary involvement, and there is no record of roentgenographic or post-mortem studies in any of the case reports.[8]

CASE REPORT

Case 8505.—H. G., white, farmer, aged 36 years. Admitted to the Halstead Hospital, October 5, 1923. The patient was born in Illinois but has spent the greater part of his life in Kansas. His general health has been excellent.

Present Illness.—His illness began early in August, 1923, and was characterized by progressively increasing weakness, susceptibility to fatigue, loss of weight, constant cough with mucopurulent expectoration, epigastric discomfort and occasional attacks of diarrhoea or constipation. He was bedridden after Sept. 15, and was brought into the clinic on a stretcher Oct. 5, 1923.

Examination.—Temp. 99.6, pulse 110, resp. 25, B. P. 105/70. Weight 125 lbs.

The patient presents the picture of advanced pulmonary tuberculosis. He is confined to his bed because of weakness, is emaciated, and coughs constantly with the production of large amounts of mucopurulent expectoration. There is nothing striking about the odor of the sputum. A careful examination fails to reveal any evidence of ulceration or inflammatory changes of any kind in the mouth or pharynx. There is diminution of resonance over the upper third of both lungs anteriorly and posteriorly, with intensification of the spoken and whispered voice. There are a few moist râles at the apices after coughing. Expiration is somewhat prolonged. The heart is negative. There is some tenderness in the epigastrium on deep palpation. Liver, spleen and kidneys not felt. The remainder of the physical examination is negative.

Laboratory Findings.—Urine: clear; acid; Sp. G. 1034; no albumin or sugar; no casts, R. B. C., or pus cells. *Stool:* negative. Repeated examinations failed to show any spirilla or fusiform bacilli. *Blood:* Wassermann, negative. Sachs-Georgi negative. R. B. C. 5,088,000; W. B. C. 18,480; Hb. 80%; C. I. 0.8. Stained smear: R. B. C. appear normal. No nucleated forms or stippling. W. B. C. seem increased in number and there is a definite eosinophilia. No pathological white cells. Platelets abundant. Differential count: (Oct. 13) 300 cells counted: P. M. Neutrophils, 34.3%; P. M. Eosinophils, 39.3%; P. M. Basophils, 0%; Large mononuclears, 2%; Transitionals, 2.3%; Large lymphocytes, 4.3%; Small lymphocytes, 17.7%.

X-ray examination.—Chest, Oct. 5 (Fig. 1). Soft spotty infiltration in upper two-thirds of both lungs except at the extreme apices, which are clear. Heart not enlarged. No abnormal mediastinal shadows. Fluoroscopic examination of the chest shows essentially the same condition. X-ray studies of the gastro-intestinal tract negative.

Sputum.—Abundant mucopurulent sputum, sometimes blood-tinged. Acid-fast stains on ten successive days failed to reveal any tubercle bacilli. When the sputum was examined several hours after collection, as is the custom in most laboratories, many varieties of bacteria were found, but no spirochaetae or fusiform bacilli. When the sputum was examined from one to two hours after collection a few spirochaetae were found but no fusiform bacilli. However, when the sputum was examined immediately after it was coughed up, it was found to be almost a pure emulsion of spirochaetae and fusiform bacilli, the organisms being morphologically identical with those seen in Vincent's angina (Figs. 2, 3). Attempts to grow the organisms were unsuccessful, possibly because treatment was instituted before the bacteriological studies were completed.

Course.—The patient received .6 gm. neoarsphenamine intravenously on Oct. 9 and .9 gm. on Oct. 13, Oct. 23 and Nov. 4. He also received 100 grains potassium iodide daily, was kept in bed and was given about 2500 calories of soft food and 2000 c.c. of fluids daily. By Oct. 15 the spirochaetae and fusiform bacilli had disappeared from the sputum, the patient was coughing less and had less pain in the abdomen. After Oct. 23 there was no more cough, expectoration or abdominal pain and the lungs were clear on physical examination.

X-ray of Chest.—Nov. 1. Lungs clear except for a small patch of infiltration, 3 cm. in diameter, near the left hilum.

Blood Examination.—Nov. 11. R. B. C. 4,672,000; Hb. 94%; W. B. C. 13,520%. Differential count: P. M. Neutrophils, 57.5%;

* Received for publication, July 22, 1924.

Fig. 1.—X-ray of the chest before treatment was begun. The film shows soft spotty infiltration of the upper half of both chests, resembling very closely the lesions of tuberculosis.

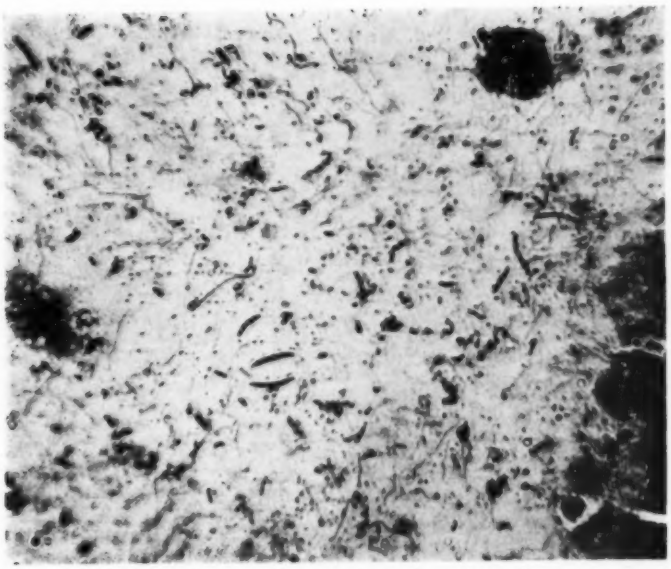

Fig. 2.—Photomicrograph of smear of sputum from our case, showing the spirochaetae and fusiform bacilli. Stained with dilute carbolfuchsin. Oil immersion.

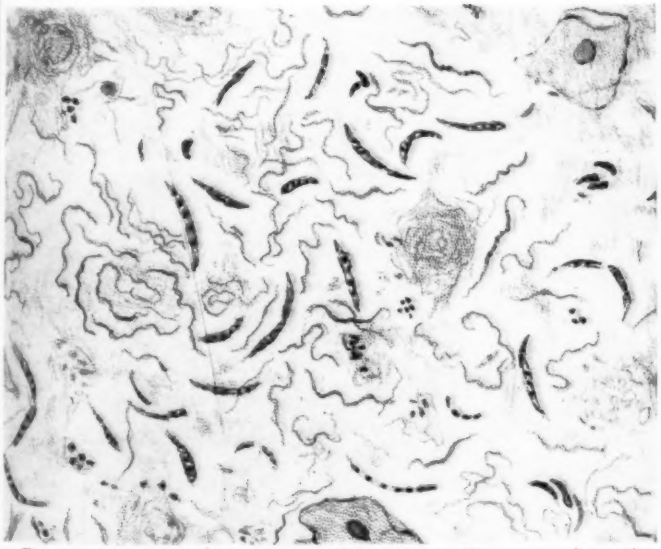

Fig. 3.—Drawing of the preparation seen in Fig. 2 to show the morphology of the organisms in greater detail. Note the great variation in size and shape of the bacilli, the beading of the bacilli and also of some of the spirochaetae.

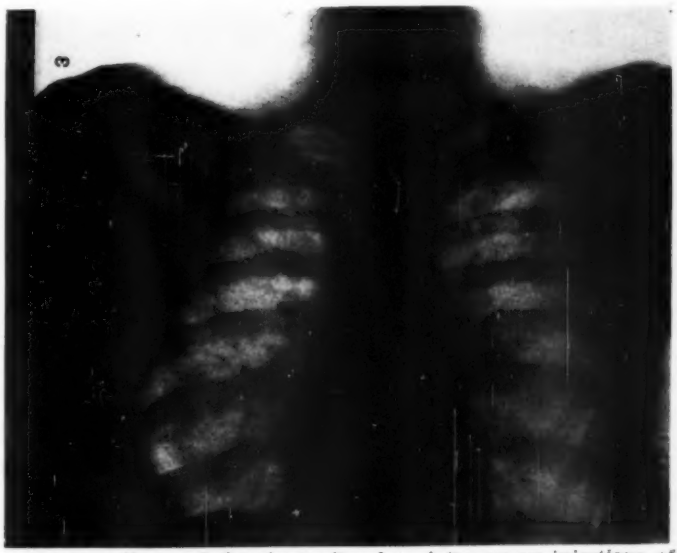

Fig. 4.—X-ray of the chest after four intravenous injections of neoarsphenamine. The lungs are now perfectly clear.

P. M. Eosinophils, 10%; P. M. Basophils, 0; Large mononuclears, 3.5%; Transitionals, 3%; Large lymphocytes, 11.5%; Small lymphocytes, 14%. Note that the eosinophilia has decreased from 39% to 10%.

X-ray of Chest.—Nov. 18 (Fig. 4). Lungs perfectly clear. All of the soft spotty infiltration seen in the first plate has disappeared.

The patient continued to improve, gained in weight and was discharged Nov. 22, apparently well. On Dec. 28 he returned to the Hospital for observation, stating that he had been working as usual and now weighed 157 lbs.—a gain of 32 lbs. since his admission to the hospital.

Blood Examination.—Dec. 28. W. B. C. 11,200. Differential count—P. M. Neutrophils, 43%; P. M. Eosinophils, 17%; P. M. Basophils, 0; Large mononuclears, 6%; Transitionals, 2%; Large lymphocytes, 6%; Small lymphocytes, 26%.

DISCUSSION

Fig. 2 shows a photomicrograph of a smear of the sputum stained with dilute carbolfuchsin; Fig. 3 shows a drawing of the same smear. It will be seen that the bacilli contain large granules, are slightly curved and vary in shape from very large organisms to mere specks. It will also be seen that some of the spirochaetae contain definite granules. It is not known whether we are dealing with two forms of the same organism or with two distinct organisms living in symbiosis. Neither is it known what the relationship is between this spirochaete and the *spirochaeta bronchialis* of Castellani which causes a bronchitis[4] and pleuritis.[5] However, attention is called to the fact that in our case the bacilli rapidly disappeared from the sputum when it was allowed to stand, leaving after an hour or two only the spirochaetae, and that an examination of the sputum made at this time might lead to an erroneous diagnosis of the *bronchopulmonary spirochaetosis* of Castellani.

Vincent's organisms have been described by Sinclair[6] and Paraf[7] as secondary invaders in pulmonary tuberculosis and pulmonary gangrene, but one wonders if their rôle is invariably secondary in these cases. Certain it is that the infection of the lung with the organisms of Vincent and with the tubercle bacillus may be clinically and roentgenologically identical, the only means of differentiation being an examination of the sputum or a therapeutic test. Certain it is, also, that the causative organisms of this disease are widely distributed throughout the entire world, and the opportunities for infection are almost omnipresent. It would be interesting to see the result of a careful examination of the sputum of all patients now being treated for tuberculosis, who do not have tubercle bacilli in the sputum.

The X-ray studies of the chest in our case showed areas of consolidation of varying density in the parenchyma of the lung, involving both upper lobes, and showing a striking similarity to the lesions seen in advanced, active pulmonary tuberculosis. The most dense consolidation was at the root areas, while at the apices there were very small patches of clear, air-containing lung; and when treatment was instituted, the root areas were the last to heal, suggesting that the disease may spread from the hilum peripheralward.

The blood showed a moderate leucocytosis and a striking eosinophilia. One cannot say whether or not the eosinophilia is a constant feature of the disease and, therefore, of some diagnostic importance, until more cases are studied. Eosinophilia is by no means a constant feature of Vincent's angina, and there is no record of differential blood counts having been made in the cases of bronchitis described in the literature.

Another feature of the disease, as illustrated in our case, is the persistent and aggravating abdominal pain, associated with alternating attacks of diarrhoea and constipation. The writer knows of a patient who developed severe gastro-intestinal symptoms, promptly died, and showed at autopsy necrosis of the lining of the entire intestinal tract, the necrotic material everywhere containing myriads of spirochaetae and fusiform bacilli. The possibility, therefore, of secondary infection of the gastro-intestinal tract from organisms swallowed in the sputum at once suggested itself, but careful examinations of the stools in our case failed to reveal any suspicious organisms and the abdominal symptoms promptly disappeared soon after treatment was begun.

In our case, the general malaise, cough, expectoration, pulmonary consolidation and gastro-intestinal symptoms disappeared after the second intravenous injection of neoarsphenamine. The patient gained 32 pounds and was hard at work two months later. He also received potassium iodide by mouth, and this drug may deserve some of the credit. Arsenic seems to be more or less a specific for all kinds of infection with Vincent's organisms, and arsphenamine appears to be the most efficacious of the arsenicals.

CASES OF BRONCHITIS IN THE LITERATURE

In 1910 Rothwell[1] reported two cases of Bronchial Vincent's Angina from Missouri. These patients had chills and fever, pain in the chest, smothering sensations and bloody expectoration. The sputum contained typical Vincent's organisms. No mention is made of the treatment, but it was two or three months before the sputum was free from the organisms. In the same article Rothwell mentions a similar case, seen by Dr. Hall of Kansas City. This patient was treated with iodides and iodine in a nebulized form, and was relieved of symptoms after several days.

Greely[2] reports the case of a patient with a bronchial infection of six months' duration, who had a chronic cough, and progressive emaciation with thirty pounds loss of weight. This patient was sent to a tuberculosis sanitorium, and in two months regained his weight. Abundant Vincent's organisms but no tubercle bacilli were found in the sputum. Greely also mentions another case with bronchial involvement. If X-ray studies had

been made, Greely's first patient might have shown definite consolidation in the parenchyma of the lung.

Campbell and Dyas [3] report seven cases of bronchitis associated with slight fever, copious expectoration, general depression and the presence in the sputum of spirochaetae and fusiform bacilli. No treatment was mentioned and the average duration was three weeks. All of these cases occured in Europe.

SUMMARY

The spirochaetae and fusiform bacilli of Vincent are widely distributed throughout the entire world, and have been known to cause a great variety of lesions in the human body, including infections of the skin, external ear, middle ear, gums, mouth, throat, gastro-intestinal tract and bronchi. To this list is added an infection of the parenchyma of the lung—a disease that may be clinically and roentgenologically indistinguishable from pulmonary tuberculosis, but which is easily diagnosed from a stained smear of the sputum, and heals like magic under intravenous salvarsan therapy. A case is reported in detail with full clinical, laboratory and X-ray studies.

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8. [Note] Since this paper was completed the writer has been told by Drs. Davis and Pilot of Chicago of several of their patients who had putrid infections of the lung—gangrene or abscess—and had Vincent's organisms in the sputum and in the material from lung puncture. Some of the patients were treated surgically and others were given sodium cacodylate.

THE USE OF ESERIN AND STRYCHNIN IN POST-OPERATIVE ABDOMINAL DISTENTION

A CLINICAL STUDY TO DETERMINE THE PROPHYLACTIC INFLUENCE OF THESE DRUGS IN THE PREVENTION OF ABDOMINAL DISTENTION FOLLOWING OPERATIONS ON THE PELVIC VISCERA, TOGETHER WITH SOME OTHER CONSIDERATIONS

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For a number of years prior to September, 1922, it had been the custom on the Gynecological Service of the Johns Hopkins Hospital to use routinely a combination of eserin and strychnin on patients who had been subjected to abdominal operations. The object of this procedure was to lessen or, if possible, to prevent entirely the not uncommon and very uncomfortable post-operative complication, abdominal distention. With this purpose in mind such patients were given, hypodermically, one-hundredth of a grain of eserin salicylate and one-fortieth of a grain of strychnin sulphate immediately on their return to the ward and every four hours thereafter for eight doses. On inquiry as to the value of this routine procedure it appeared to be the general impression that the incidence of post-operative tympanites was markedly lessened or its course attenuated by the use of these drugs as compared with the periods before their adoption. However, the writer was unable to obtain any specific information based on the observation of a series of controlled cases in regard to the influence actually exerted by these drugs in lessening post-operative distention.

This form of post-operative prophylaxis is recommended in some of the standard textbooks of surgery,[1,2,3,4] bearing on the treatment of post-operative complications, and in some of the many clinical articles [5,6,7] devoted to this important subject. The use of eserin seems to be correct in its conception, for one of its pharmacological properties is the stimulation of intestinal peristalsis.[8,9] The employment of strychnin is probably based upon its action in increasing the reflex activity of the spinal cord. However, the action of eserin on the intestines is said to depend upon its effect on the terminations of the parasympathetic nerves in these viscera. Hence it does not seem clear why strychnin is used with eserin, nor is it easy to grasp the rationale for the use of combinations of eserin and atropin which are recommended by some authors [3] for the same purpose. Experimental evidence would indicate that eserin and pilocarpin are drugs particularly suited to increase the tone and to stimulate the rhythmical movements of the intestine. The work of Cannon and Murphy [10] on "dynamic ileus," as they term their experimentally produced phenomena, demonstrated the independence of the rhythmical intestinal movements

when freed from the influence of the central nervous system, and that the inhibition of the normal intestinal motion following manipulation is probably a purely local phenomenon and not dependent on inhibitory stimuli from the splanchnic nerves. They also described the rapid and transient effect of eserin on the intestines of their experimental animals in which "dynamic ileus" had been produced reflexly, and suggested that this drug would probably be of value in this type of ileus alone. The work of Gunn and Underhill [11] on the intestines of mammals and of Gunn and Whitelocke [12] on the movements of the isolated human vermiform appendix demonstrated the ability of these structures to survive low temperatures for various time intervals, while still exhibiting apparently normal rhythmical movements and still retaining the capacity to react characteristically to the action of various drugs. These investigators used pilocarpin as the chemical with which to produce stimulation of the receptive substance at the termination of the parasympathetic nerves. Gunn and Whitelocke [12] observed that a segment of human appendix immediately adjacent to a ruptured gangrenous portion exhibited no conspicuous impairment of spontaneous movement. According to Cross,[13] the segments of the isolated human appendix vermiformis react very sluggishly to physostigmin or pituitrin when used alone. However, a very short time after either drug has been employed alone, an application of the other will produce a pronounced effect. Cross, therefore, considers the combined effect of the physostigmin and pituitrin as a synergistic phenomenon and recommends their use clinically. Their clinical efficiency he illustrates by reporting fifteen cases in all of which the combination of physostigmin and pituitrin relieved the signs and symptoms of intestinal atony after more palliative measures had failed. In ten of his cases, however, Cross did not carry out proper controls, so that one has no way of estimating the probable effect of each drug used separately before resorting to their combined administration.

With so much suggestive experimental evidence of which only a fragment has been quoted, and so little properly controlled clinical study with which to test the probable applicability of these laboratory results, we felt that such an investigation as the present one would not be amiss. The object of this study, therefore, was to obtain, if possible, some specific information as to the actual value of eserin and strychnin in lessening or preventing post-operative tympanites in patients who had been subjected to abdominal operations on the pelvic organs, while *under ether anaesthesia.* Despite the limitations to which such a study is subject, we felt that, when properly controlled, it would have a definite clinical value.

PLAN OF STUDY

A total of 162 cases were studied over a period of eleven months during the years 1921-22. The patients were all on the gynecological service of the Johns Hopkins Hospital and *had all been subjected to major abdominal operations under ether anaesthesia.* Eserin salicylate (gr. 1/100) and strychnin sulphate (gr. 1/40) were given hypodermically to each alternate patient immediately on her return to the ward after operation and every four hours thereafter for eight doses. Of the 162 patients studied, 74 received these drugs and 88 did not. The former will be referred to as the treated patients and the latter as the untreated. The patients studied were all from one ward, under the supervision of the same surgeon. The pre-operative as well as post-operative care, with minor exceptions, was the same in all, except in cases of peritonitis. There are necessarily many factors which make it impossible that the same conditions should prevail in every case, but these have all been noted and will be referred to specifically further on. The influence of the technic of the various operators is at first sight an important question, but all of the six surgeons who took part in these operations were trained in one clinic and with minor variations employed a uniform technic. The least experienced surgeon of the group had had four years of preliminary training. Nevertheless, the human equation is a variable factor and only one of several which make perfectly constant conditions impossible in such a clinical study.

The 162 cases studied do not represent all the operative cases from the service but only those from one twelve-bed ward, and no patients are included who had perineal operations unless the latter were associated with abdominal surgery. Observations were recorded in regard to abdominal distention, nausea, vomiting, blood pressure, pulse rate, time of first voluntary micturition, type of operation performed, operative complications, inflammatory conditions prevailing at operation and so on. Notations as to abdominal discomfort were made at first but later abandoned because of the subjective nature of such a condition and the possibility of a biased opinion influencing the observers as the investigation progressed. Observations, other than those by the nursing staff, were made on the patient's return to the ward, again four hours later and then at intervals of two hours up to the tenth hour after operation. The next observation was made six hours later and then every eight hours thereafter, until ninety-six hours after operation. In numerous cases, when the condition indicated, observations were made more frequently and over a much longer period of time.

For the purpose of tabulation the cases have been divided into seven groups according to the type of operation performed. Any exceptions are noted. The incidence of post-operative distention and emesis, and the time of the first voluntary micturition, were studied in each of these groups. The first and last are the conditions which are said to be particularly favorably influenced by the use of eserin and strychnin. In describ-

ing the degree of distention or the severity of post-operative vomiting the terms *moderate, marked* and *very marked* have been used. These gradations are purely descriptive, arbitrary and naturally subject to individual bias. These patients were all examined by the writer before as well as after operation, and particular attention was given to the contour of the anterior abdominal walls and the level of hepatic dullness. Accurate post-operative measurements were not feasible, because of the abdominal dressings which reached from the pubes to the epigastrium. However, the writer feels that no bias entered into this study, it being undertaken merely to ascertain the facts, whatever they might be. The actual results were unknown until the individual observations had been grouped and tabulated as shown in the following pages.

GROUP I.—*Patients from whom the uterus and the adnexa from one or both sides were removed.*

There are 76 patients in this group, 41 of whom received no eserin and strychnin and 36 who did. *Distention* developed in 22 patients. Of the group which did not receive eserin and strychnin nine (22 per cent) and of the group receiving eserine and strychnin thirteen (36 per cent) developed post-operative tympanites for various periods and of different degrees (Table I).

TABLE I.

The duration and degree of distention in the distended patients of Group I.

	DISTENTION				Average number hours per patient having distention
	Moderate (hrs.)	Marked (hrs.)	Very marked (hrs.)	Total (hrs.)	
Patients not receiving E. and S., (9)	16	50	50	116	12.8 hrs.
Patients receiving E. and S., (13)	24	230	100	354	27.2 hrs.

The figures in the above table bring out the comparatively greater degree and longer duration of the distention in the patients receiving the prophylactic treatment as compared with those who did not—a difference of more than 2 to 1. This difference in the severity of the distention is even more striking when one notes that the difference in the incidence in the treated and non-treated groups was 1.6 to 1.0 (36 per cent and 22 per cent). It should also be mentioned that 19 of the patients included in Group I had a well marked pelvic peritonitis, many of them having free pus in the pelvic portion of the peritoneal cavity. Of these, five received the prophylactic treatment. Four of this five developed distention, of marked or very marked degree, totalling 96 hours. Of the remaining 14 patients, none were given eserin and strychnin and only two developed tympanites. In one of these the distention was of moderate and marked degree and lasted four hours. In the other, a patient suffering from a generalized tuberculous peritonitis, there was marked distention for 40 hours—a total of 44 hours of distention for these patients with peritonitis who were not treated with eserin and strychnin.

Emesis of more than transient occurrence was noted in 22 patients of Group I, occurring in fourteen (34 per cent) of the untreated and in nine (25 per cent) of those receiving the prophylaxis. The number of hours and the varying degrees of emesis are given in Table II.

TABLE II.

The duration and degree of emesis in the vomiting patients of Group I.

	EMESIS				Average number hours per patient having emesis
	Moderate (hrs.)	Marked (hrs.)	Very marked (hrs.)	Total (hrs.)	
Patients not receiving E. and S., (14)	95	0	12	107	7.6 hrs.
Patients receiving E. and S., (9)	31	14	4	49	5.4 hrs.

It will be noted from the above table that emesis was a more frequent complication and of somewhat longer average duration in the untreated than in the treated patients.

The time of the re-establishment of voluntary micturition is tabulated in Table III.

TABLE III.

Number of hours after operation after which voluntary micturition was re-established (Group I).

	HOURS AFTER OPERATION																No. of pts.
	4	6	8	10	16	24	32	40	48	56	64	72	80	88	96	112	
No E. & S.	1	3	6	2	5	7	8	1	3	3	0	0	0	0	1	1	41
E. & S.	2	3	4	4	4	3	5	2	1	0	2	2	1	1	1	0	35

The early occurrence of voluntary micturition is particularly important in gynecological patients, for catheterization of our patients is performed every eight hours after operation until the patients can void voluntarily once or oftener within that period. In Table III, it may be seen that during the first twenty-four hours after operation twenty-four (58.5 per cent) of the untreated and twenty (57.1 per cent) of those treated voided voluntarily. By the end of 48 hours, 87.8 per cent and 80 per cent, respectively, were able to micturate voluntarily and thereby avoid further catheterization. It may be of interest to note that the patient who did not void until after the end of 112 hours was one who had undergone a panhysterectomy for carcinoma of the cervix uteri, while the patient with tuberculous peritonitis, mentioned earlier as having such prolonged abdominal distention, voided by the end of the sixth hour.

GROUP II.—*Patients upon whom a hysteromyomectomy was performed.*

There are 26 patients in this group, 17 of whom received and 9 who did not receive the prophylactic eserin and strychnin treatment. *Distention* occurred in 10 patients, all of whom had received eserin and strychnin, so that in this entire group, 58.8 per cent of the treated patients were the only ones distended. The duration and the degree of distention in these 10 patients are tabulated in Table IV.

TABLE IV.

The duration and degree of distention in the distended patients of Group II.

	DISTENTION				Average number hours per patient having distention
	Moderate (hrs.)	Marked (hrs.)	Very marked (hrs.)	Total (hrs.)	
Patients not receiving E. and S., (0)	0	0	0	0	0 hrs.
Patients receiving E. and S., (10	32	72	52	156	15.6 hrs.

Emesis sufficient to warrant notation occurred in seven (41 per cent) treated patients in this group and was absent in the others. The results of these observations are recorded in Table V.

TABLE V.

The duration and degree of emesis in vomiting patients of Group II.

	EMESIS				Average number hours per patient having emesis
	Moderate (hrs.)	Marked (hrs.)	Very marked (hrs.)	Total (hrs.)	
Patients not receiving E. and S., (0)	0	0	0	0	0 hrs.
Patients receiving E. and S., (7)	38	4	24	66	9.4 hrs.

The time of re-establishment of *voluntary micturition* is tabulated in Table VI.

TABLE VI.

Number of hours after operation after which voluntary micturition was re-established (Group II).

	HOURS AFTER OPERATION												Patients
	4	6	8	10	16	24	32	40	48	56	64	136	
Patients not receiving E. and S.	—	—	—	2	4	1	1	1	—	—	—	—	9
Patients receiving E. and S.	—	3	3	—	2	3	1	2	—	1	1	1	17

From Table VI it will be noted that of the non-treated patients seven (77.7 per cent) voided voluntarily by the end of 24 hours, while during the same period eleven (64.7 per cent) of those treated with eserin and strychnin were able to void. Two of the untreated patients had untoward operative or post-operative experiences. One of them took the anesthetic very badly. The operation was prolonged and especially difficult, because of a large myomatous uterus which was almost molded in the pelvis and a large tumor on the anterior distal uterine aspect that had developed behind the bladder. This patient voided within 32 hours after operation. The other woman also had a difficult operative condition, due to numerous dense post-operative adhesions resulting from a previous laparotomy performed elsewhere. She left the operating table in a state of surgical shock. Sixteen hours after operation she developed bronchopneumonia, but had an otherwise uncomplicated surgical recovery except that voluntary micturition did not occur until 40 hours after operation.

GROUP III.—*Patients with chronic salpingitis from whom both Fallopian tubes, with or without one ovary, were removed, the uterus and remaining ovary or ovaries being left.*

This group comprises 27 patients, of whom 13 did and 14 did not receive the prophylactic treatment. *Distention* occurred only in the treated patients, five (38 per cent) of these being involved. (Table VII.) Three women in Group III who were not treated deserve particular mention. Two of these patients who had ovarian cysts were grouped with the chronic salpingitis patients, because a tube and ovary were removed. No culturally demonstrable infection was present, but we did not wish to create an additional group for these two isolated cases. One of the two had a huge, adherent cystadenoma of the left ovary and following its removal many surfaces denuded of peritoneum remained. The second patient had a large ruptured ovarian cystadenoma. The third had an uncontrollable hemorrhagic ooze from the pelvic wall, after removal of an adherent ovary, necessitating the employment of a raw gauze pelvic drain to stop the bleeding. None of these three patients developed any abdominal distention.

TABLE VII.

The duration and degree of distention in the distended patients of Group III.

	DISTENTION				Average number hours per patient having distention
	Moderate (hrs.)	Marked (hrs.)	Very marked (hrs.)	Total (hrs.)	
Patients not receiving E. and S., (0)	0	0	0	0	0 hrs.
Patients receiving E. and S., (5)	4	16	72	92	18.5 hrs.

Emesis of noteworthy degree occurred in six (42.8 per cent) of the untreated and in seven (53.8 per cent) of the treated patients (Table VIII).

TABLE VIII.

The duration and degree of emesis occurring in the vomiting patients of Group III.

	EMESIS				Average number hours per patient having emesis
	Moderate (hrs.)	Marked (hrs.)	Very marked (hrs.)	Total (hrs.)	
Patients not receiving E. and S., (6)	9	2	0	11	1.8 hrs.
Patients receiving E. and S., (7)	17	42	24	83	11.8 hrs.

The time of the first *voluntary micturition* is tabulated in Table IX.

TABLE IX.

Number of hours after operation after which voluntary micturition was re-established (Group III).

	Hours after operation													Patients
	4	6	8	10	16	24	32	40	48	56	64	72	96	
Patients not receiving E. and S.	—	2	1	1	2	4	1	—	—	—	1	1	1	14
Patients receiving E. and S.	0	0	2	2	1	4	2	1	—	—	1	—	—	13

From Table IX it will be seen that ten (71.4 per cent) of the untreated and nine (69.2 per cent) of the treated patients voided voluntarily within 24 hours after operation.

Group IV.—*Patients with subacute salpingitis without free pus in the pelvis, treated by bilateral salpingectomy without drainage and with or without the removal of one ovary.*

Six patients come under this heading; four received and two did not receive the eserin and strychnin treatment. *Distention* occurred only among the treated patients, three (75 per cent) suffering from it for a total of fifty-eight hours—moderate, 7 hours; marked, 8 hours; very marked, 43 hours—so that each of these patients had an average of 19.3 hours of distention.

Emesis occurred in one (50 per cent) of the untreated and in three (75 per cent) of the treated patients, as recorded in Table X.

TABLE X.

The duration and degree of emesis in the vomiting patients of Group IV.

	Emesis				Average number hours per patient having emesis
	Moderate (hrs.)	Marked (hrs.)	Very marked (hrs.)	Total (hrs.)	
Patients not receiving E. and S., (1)	1	1	0	2	2 hrs.
Patients receiving E. and S., (3)	12	11	12	35	11.6 hrs.

Voluntary micturition was re-established in the two untreated patients within six and sixteen hours, while in the treated patients it first occurred within sixteen hours in two, within twenty-four hours in one, and in the fourth within thirty-two hours after operation.

Group V.—*Patients with subacute salpingitis and purulent pelvic peritonitis treated by bilateral salpingectomy with or without the removal of one ovary.* (Pelvic drainage through the vagina was employed in all but four patients.)

Inasmuch as all the women in this group were suffering from a purulent pelvic peritonitis probably with varying degrees of contamination of the general abdominal cavity following operation, it was considered inadvisable to try the effects of eserin and strychnin upon them. They therefore received the usual treatment for peritonitis, being given repeated doses of morphin, from two to three liters of physiological salt solution every twenty-four hours by hypodermoclysis and nothing by mouth for varying periods of time, according to their condition. In this group of seventeen patients *distention* occurred in two (11.7 per cent). The distention was moderate for 8 hours and marked for 23 hours, totalling 31 hours of distention or an average of 15.5 hours per patient. In one of these two patients the distention began at the sixteenth hour, was of marked degree and lasted three hours but did not recur. In the other patient distention began at the same time, was moderate in degree and lasted four hours. Twenty-four hours later it recurred and persisted for twenty-four hours more before finally and permanently disappearing.

Emesis occurred in three patients (17.6 per cent), was only moderate in degree, and totalled 6 hours or an average of two hours per patient.

The re-establishment of *voluntary micturition* is given in Table XI.

TABLE XI.

Number of hours after operation after which voluntary micturition was re-established (Group V).

	Hours after operation									Patients
	4	6	8	10	16	24	32	40	80	
Patients not receiving E. and S.	2	1	3	—	4	3	2	1	1	17

From Table XI it is seen that thirteen (76.4 per cent) of the patients in this group voided voluntarily within twenty-four hours after operation.

Group VI.—*Patients with ruptured tubal pregnancies from whom one tube or a tube with the corresponding ovary was removed.*

Of the six patients in this group, four (66.6 per cent) did not receive and two (33.3 per cent) were given the eserin and strychnin treatment. *Distention* was observed only in the two patients (100 per cent) who had received eserin and strychnin, the duration in both being about the same. The distention was moderate for 34 hours, marked for 30 hours, and very marked for 12 hours, altogether totalling 76 hours, or an average of 38 hours per patient. It should be noted that one of the untreated patients was in a state of profound shock after operation, necessitating transfusion, but that an uneventful convalescence followed.

Emesis of moderate degree for a period of two hours occurred in one (25 per cent) of the untreated patients.

The re-establishment of *voluntary micturition* is shown in Table XII.

TABLE XII.

Number of hours after operation after which voluntary micturition was re-established (Group VI).

	HOURS AFTER OPERATION												Patients
	4	6	8	10	16	24	32	40	48	56	64		
Patients not receiving E. and S.	—	1	—	—	2	1	—	—	—	—	—		4
Patients receiving E. and S.	—	—	—	—	—	—	—	1	—	—	1		2

From Table XII it will be seen that four (100 per cent) of the untreated patients voided voluntarily within twenty-four hours after operation, the patient previously mentioned as being in a state of profound shock after operation voiding within sixteen hours. Neither of the two treated patients voided within the twenty-four hour period.

GROUP VII.—*Patients on whom only a modified Gilliam suspension of the uterus was performed.*

Of the four patients in this group three received and one did not receive prophylactic eserin and strychnin treatment.

Distention occurred only in the treated group, one patient (33 per cent) suffering from it to a marked degree for 40 hours.

Emesis of moderate degree and of about 4 hours' duration occurred in one (33.3 per cent) of the treated patients and also in the patient who was not treated.

Voluntary micturition commenced within four hours after operation in the untreated patient; in the three who were treated within 24, 32 and 56 hours, respectively.

Relations between distention, emesis, and delayed voluntary micturition.

Although one would offhand expect a rather close relationship between the occurrence of abdominal distention and emesis, the facts do not permit of such a ready generalization, for of the 45 patients with distention, twenty (44.4 per cent) suffered from emesis as an added complication. On the other hand, of the 53 patients in whom vomiting was a complication, in twenty (37.7 per cent) it was associated with distention. Expressed conversely, 55.6 per cent of the patients suffering with distention had no noteworthy post-operative vomiting, while 62.3 per cent of those who had noteworthy post-operative emesis were not troubled with tympanites. In this particular relation, no definite difference could be noted between the treated and untreated patients.

The influence of nausea and vomiting upon voluntary micturition is not very clear. Generally speaking in the patients who had prolonged vomiting or distention beginning soon after operation, we noted a marked delay in voluntary micturition. However, there are notable exceptions, and when one compares the occurrence of voluntary voiding in patients having the complications of nausea and vomiting with that in those who did not have the two latter complications, one finds a group in whom delayed voiding cannot be attributed to post-operative tympanites or emesis or to recognizable operative accidents. Unsatisfactory as this conclusion is, we can only present the facts and be governed by them.

The influence of gauze coming in contact with the peritoneal surfaces at operation has also been considered in this study, and to our surprise we are unable *clinically* to support the theory that moist gauze in contact with serous surfaces produces post-operative intestinal distention. Every patient in this study, except three of the four on whom a modified Gilliam suspension of the uterus was performed, had one or more large pieces of warm, moist, abdominal gauze used in the peritoneal cavity, and this fact is to be borne in mind when considering our findings in this study. Of the patients upon whom only a modified Gilliam suspension of the uterus was performed, only one developed post-operative distention and in her case no gauze had come in contact with either the parietal or visceral serosa. Despite these findings, we do not practice the indiscriminate use of gauze in the peritoneal cavity, but try to employ as little as possible or to avoid its use altogether. In fact, during the past year our staff, at the request of Dr. Cullen, have used methods in which gauze, when used intra-abdominally, did not come in contact with the intestinal surfaces, and we still feel that all trauma to serous surfaces should, as far as possible, be scrupulously avoided. The query naturally arises: What would have been the results had no gauze been used in the peritoneal cavities of the patients in this study? This we cannot answer. Parenthetically, however, it may be noted that after these observations had been made, I had a patient in whom both ovaries, represented by large dermoid cysts, (one with a twisted pedicle) were removed with the tubes. The uterus, containing about a three months' viable pregnancy, which was later expelled, was left *in situ*. No gauze came in contact with the serous surfaces and this patient died of a paralytic ileus, the cause of which was not explained at autopsy, the serous surfaces being everywhere pale grey, smooth, and glistening.

Contact of the intestine with iodine painted on the skin is a factor which has been stressed by numerous writers as a cause of post-operative tympanites. This point has been carefully controlled for certain patients in this study on whom uncomplicated operations were performed. Post-operative tympanites was also a complication here, but only in some of those patients that had received the prophylactic treatment with eserin and strychnin.

Surgical shock occurred in eight patients, being due to hemorrhage in every case and characterized by hypotension, extreme tachycardia (when the pulse was palpable) and profound prostration, together with the other clinical signs associated with this syndrome. The influ-

ence of this complication in the production of post-operative distention is rather difficult to estimate, the small number of cases preventing the deduction of any definite conclusion. It should be stated, however, that four of these eight patients developed very marked post-operative distention, i. e., in Case 1 distention commenced 24 hours after operation, voluntary micturition beginning at the same time. In Case 2 bronchopneumonia developed after 16 hours; distention began after 56 hours and voluntary micturition occurred after 71 hours. These two patients had received the eserin and strychnin treatment while the two following had not. In Case 3, bronchopneumonia developed at about the 14th hour, voluntary micturition occurred towards the end of the fortieth hour and distention after 48 hours. In Case 4 acute gastric dilatation developed (clinically) after 64 hours, and the patient voided voluntarily within 112 hours after operation. The remaining four patients, of whom one was treated and the other three not, had no distention. Emesis occurred in none except the one in whom acute gastric dilatation was a complication. Voluntary micturition in these four patients occurred within 16, 24, and 48 hours (two patients), after operation, the woman who voided by the twenty-fourth hour being the one who had been treated with eserin and strychnin.

The time of onset of post-operative distention in those so affected, is of interest. In 72 per cent of the untreated group it developed between the sixteenth and twenty-fourth hour after operation, while during the same period 47 per cent of the treated patients became distended. The remaining patients with distention in general tended to develop this complication soon after the twenty-fourth hour, the incidence decreasing proportionately as the time after operation increased, so that after the sixty-fourth hour none of the patients in this study developed tympanites. The earliest that any patient in this study developed distention was six hours after operation.

The story of *post-operative emesis* is an entirely different one, and strange to relate, conforms more or less to our general impression of this complication, for in other ways general impressions have so often proved to be erroneous, as is well exemplified in our study. Briefly, the majority of both treated and untreated patients that suffered from emesis as a complication developed it during the first four hours after operation, this being true in 74 per cent of the untreated and in 59 per cent of the treated patients. The tendency for emesis to develop diminishes abruptly after the fourth hour after operation and in none of the patients did it develop as the sole gastro-intestinal complication after the sixteenth hour. In the few instances in which it occurred after this time it was associated with marked post-operative distention. In one patient, in whom distention and vomiting developed sixty-four hours after operation the condition was considered, clinically, to be due to acute gastric dilatation, since the usual signs and symptoms, which are considered to be diagnostic, were present.

The effect of eserin and strychnin upon blood pressure. In comparing the blood pressure of the two groups of patients in this study we are unable to demonstrate any definite influence exerted by eserin and strychnin. In order to determine whether patients with post-operative hypotension who were to receive the eserin and strychnin treatment had a pressor mechanism that would respond to stimulation, we tried the effect of ten minims of 1-1000 adrenalin hydrochloride hypodermically upon four, in each instance obtaining a well marked response as indicated by blood pressure determinations taken at sixty-second intervals. The responses were rapid, the blood pressure rising definitely within 90 to 120 seconds, reaching within three to four minutes a maximum which was sustained for four or five minutes, only to subside rather rapidly to the level existing before the injection of adrenalin, the entire reaction covering a period of from twelve to fourteen minutes.

The *rôle of anesthesia* in this study can be noted only in one connection, but this is probably worthy of mention. During the first two and a half months of this study the method of administering anaesthetics was changed. During the first part of this period anaesthesia was given by internes under the more or less disinterested supervision of an assistant resident. Then followed a transition period in which anaesthesia began to be undertaken by graduate nurses. These new anesthetists, although highly trained and competent, had, however, never given anesthesia for the gynecological phase of abdominal surgery, and therefore required some time to become experts in this branch. Thus, for a period of several weeks, the anesthesia was not altogether satisfactory, but after this "period of initiation," as it might be called, the anesthesia problem, which for years had been a matter of more or less concern for the operator, practically ceased to exist. During this transition period twenty-nine (39.1 per cent) patients treated with eserin and strychnin were operated upon. Of this number eighteen (62. per cent of the 29) developed post-operative abdominal distention. Of the total 34 treated patients who developed distention, 52.6 per cent had this complication during the first two and one-half months' period of this study, which represents the transition stage in the management of our anesthetics. The untreated patients during this same period numbered 19 (27.2 per cent of this entire untreated group). Of these, three (15.7 per cent) developed distention. Of the total 11 untreated patients who developed distention, 21.5 per cent were encountered during the first two and one-half months of this study. These figures are rather startling, particularly in regard to the treated group, but not more so than the actual observation of the patients during and after this period of transition which marked the change in the personnel of those in charge of our anes-

thesia. In no other period of our study was there such a fluctuation in the incidence of post-operative distention. Hence, we feel that among the many factors involved in the causation of post-operative tympanites, anesthesia improperly or unskillfully administered plays an important rôle.

SUMMARY

The present study includes 162 gynecological patients, upon whom an abdominal operation was performed. Of these, 74 received eserin and strychnin after operation and 88 did not. Of the patients who received eserin and strychnin after operation, thirty-four (45.9 per cent) developed *distention* totalling 776 hours, or an average of 22.8 hours of distention for each patient. Of the patients who did not receive the prophylactic treatment of eserin and strychnin, eleven (12.5 per cent) developed post-operative *distention* totalling 147 hours, an average of 13.4 hours for each patient.

Emesis occurred as a complication in twenty-seven (35.1 per cent) of the treated patients, while in the untreated group, twenty-six patients (29.5 per cent) developed this condition.

Voluntary micturition was re-established within twenty-four hours after operation in forty-four (59.4 per cent) of the treated patients and in sixty-one (69.3 per cent) of those who were not treated.

In studying the relation between post-operative *distention, emesis and delayed voluntary micturition,* no definite difference was found between the treated and untreated groups.

We have been unable in this particular study to substantiate clinically the theory that the use of *gauze in the peritoneal cavity* during pelvic operations is a cause of post-operative tympanites. However, no controls are available in this study for this particular observation, so that conclusions are not permissible.

No definite conclusions can be formulated from this study concerning the comparative post-operative course of treated and untreated patients in whom *operative shock* from hemorrhage was a complication.

Of the untreated patients who suffered from *distention* 81.8 per cent developed this complication within twenty-four hours after operation, while in the treated group this was true in 61.7 per cent of the patients. There appears, however, to be a more marked tendency for distention to develop earlier after operation as well as at a more remote time in the treated patients than in those not treated.

Emesis as a complication occurred, in the majority of the patients so afflicted, during the first four hours after operation.

No definite effect upon *blood pressure* could be noted from the use of eserin and strychnin.

The rôle of *anesthesia* as a factor in the causation of post-operative tympanites is probably an important one, for while the incidence of distention among the treated patients for the period of the entire study is 45.9 per cent, its incidence during the two and one half months' period when the anesthetics were not so well given was 62 per cent and its incidence after this period when satisfactory anesthesia was established was 35.5 per cent. In the untreated group the percentages are respectively 12.5, 15.7 and 11+ per cent.

In conclusion we may say that *we have not been able to demonstrate any benefits to be derived from the post-operative use of eserin and strychnin,* as described, in abdominal operations on the pelvic viscera. In fact, paradoxical as it may seem, post-operative complications such as emesis, delayed voluntary micturition, and particularly distention, appear to occur more frequently in patients treated prophylactically with eserin and strychnin than in those not so treated, and its use, therefore, has been abandoned on the gynecological service of The Johns Hopkins Hospital.

We also think that in a clinical study such as this, one is not warranted in hypothesizing a series of possible explanations which might seem to render our observation more compatible with accepted clinical usage, known pharmacological actions or experimental results as applied to human subjects. We feel that our observations on this series of patients have been as well controlled as is possible clinically, and that they have extended over an interval sufficiently long to render possible the careful observation of a few patients at a time.

It would be most ungrateful of me not to acknowledge the never failing kindness and co-operation of Dr. Cullen in permitting this study.

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AN EXPERIMENTAL STUDY OF UNUNITED FRACTURES WITH ESPECIAL REFERENCE TO THE INORGANIC BONE-FORMING ELEMENTS IN THE BLOOD SERUM

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Most of the observers that have undertaken an experimental study of the non-union of fractures have confined themselves mainly to modes of therapy for combating the condition. Very little animal experimentation has been done. In a previous clinical study of ununited fractures [1] it was demonstrated that in many patients with non-union there was, as an underlying basis, a constitutional disturbance and that this consisted in a deficiency in either the calcium or the phosphorus content of the serum. In most instances the amount of phosphorus was found to be low. Especial emphasis was placed upon the calcium and phosphorus product (obtained by multiplying the calcium by the phosphorus content, both in mgms. per 100 c.c. of serum)* and its relation to the healing fracture. The optimal product for healing in normal fractures was found to be between 35 and 40, whereas, in many patients with an ununited fracture, the product was below 30. This latter product was concluded to be entirely inadequate for bone healing. In order to substantiate this conclusion the following experiments were undertaken.

In these studies the method of procedure was as follows: first, to determine the normal calcium and phosphorus content in the serum of the dog; next, to place a certain number of these animals on a diet calculated to reduce the phosphorus content of the serum; and finally, to produce fractures and observe healing. To establish a norm for the dog, the calcium and phosphorus content of the blood serum of twenty stock animals was determined. The calcium analyses were made by the method of Kramer and Tisdall,[2] those for phosphorus by the Briggs [3] modification of the Bell-Doisy method. These same methods were used in the clinical study.[1] As may be seen in Table I, the calcium analyses were fairly constant, the lowest being 9.0 mgms. per 100 c.c. of serum and the highest 10.7, with an average of 10.12. The phosphorus content of the serum had a much wider variation, from 4.0 mgms. per 100 c.c., the lowest, to 7.7 the highest, with an average of 6.0. Those that had the low phosphorus figures, were, as a general rule, older animals.

TABLE I.

The calcium and the phosphorus content of the serum of normal dogs in mgms. per 100 c.c. of serum.

Dog	Calcium	Phosphorus	Product of calcium and phosphorus
No. 1	10.2	6.2	63.2
No. 2	10.4	5.2	54.
No. 3	10.5	6.8	61.4
No. 4	10.1	4.5	45.4
No. 5	10.1	7.7	77.7
No. 6	10.5	4.8	50.4
No. 7	10.2	7.6	77.5
No. 8	9.1	6.5	59.1
No. 9	10.3	5.9	60.7
No. 10	9.7	6.3	61.1
No. 11	9.9	4.5	44.5
No. 12	10.3	6.0	61.8
No. 13	10.7	4.8	51.3
No. 14	10.5	7.3	76.6
No. 15	10.1	6.4	64.6
No. 16	9.0	4.0	36.
No. 17	10.2	5.5	56.1
No. 18	10.0	5.7	57.
No. 19	9.7	7.1	68.8
No. 20	10.6	8.8	93.2
Average	10.1	6.0	60.6

After the normal had been determined, ten young healthy animals were selected for experiment. In Table II are given the calcium and the phosphorus content of the

* This product is purely empirical and has no chemical significance.

serum in these animals on October 1, 1923. The average calcium content of the serum was 10.3 mgms. per 100 c.c. and the average phosphorus 6.7 mgms. with an average product of 69.0.

TABLE II.

The calcium and the phosphorus content of the serum of ten normal dogs on Oct. 1, 1923, before they were put on Diet 1.

Dog	Calcium	Phosphorus	Product
No. 1	10.2	6.2	63.9
No. 2	10.5	6.8	71.8
No. 3	10.1	6.7	78.4
No. 4	10.2	7.6	77.8
No. 5	9.1	6.5	59.9
No. 6	10.3	5.9	61.4
No. 7	10.5	6.3	66.9
No. 8	10.3	6.0	62.3
No. 9	10.5	7.3	77.6
No. 10	10.2	6.4	65.2

On October 2, 1923, these dogs were put on the following diet suggested by Dr. E. V. McCollum:

DIET 1.

White bread	200 grams
Milk, skimmed	100 c.c.
Meat (liver)	10 grams
Sodium chloride	1.0 gram
Calcium carbonate	0.3 gram

These constituents in these amounts were given for every one and one half kilograms of body-weight. This diet is below the optimal in both calcium and phosphorus, and contains about equal amounts of these elements. It is very low in Vitamin A, and is lacking in the antirachitic substance, Vitamin D. No especial difficulty was experienced in getting the animals to eat this diet after the first few days. They lost slightly in weight during the first two weeks on the diet, but after this initial loss their weights were fairly constant.

The calcium and the phosphorus content of the serum were determined at weekly intervals. No changes became apparent until about the fourth week, when a lowering of the phosphorus was noted. This decrease became more striking at the end of the sixth week (Table III).

TABLE III.

The calcium and the phosphorus content of the serum of young dogs after six weeks of Diet 1. (In mgms. per 100 c.c. of serum.)

Dog	Calcium	Phosphorus	Product
No. 1	10.0	5.8	58.0
No. 2	8.9	3.6	32.0
No. 3	9.8	4.7	46.0
No. 4	9.8	3.7	32.2
No. 5	10.3	5.3	54.5
No. 6	9.4	3.9	36.6
No. 7	10.5	5.9	62.4
No. 8	10.8	4.2	45.9
No. 9	10.5	6.0	63.5
No. 10	9.8	3.8	37.5

The most striking result is shown in Dog 2, the serum phosphorus of which was reduced from 6.8 to 3.6. Scarcely any reduction was noted in Dogs 1, 3, 5, 7 and 9. It is interesting to observe that the radiograms of these animals, except that of Dog 1, indicate that the epiphyses are still ununited, whereas in the others, which have a marked reduction in the phosphorus, the epiphyses have united. From this it would seem that the young dog, before the epiphyses have united, is not so readily affected by dietary change as is the older animal.

On November 16th, the bones of the foreleg in Dog 1, and Dog 2 were fractured. Dog 1 was used as a control and placed on the regular diet of the stock animals, which consists of corn bread and lungs, a diet high in phosphorus and low in calcium. In order to make up for the calcium deficiency, three grams of calcium carbonate were added to the daily diet. Dog 2 and the other eight animals were then changed to Diet 2, which is made up on a percentage basis. This obviated the necessity for the weighing of each individual diet.

DIET 2.

Rolled oats	40 per cent
Gelatine	10 per cent
Wheat gluten	17 per cent
Sodium chloride	1 per cent
Calcium carbonate	3 per cent
White flour	36 per cent
Butter	2 per cent
Orange juice	5 c.c.

This diet is poor in phosphorus and high in calcium. It was calculated to reduce the phosphorus content still further. McCollum, Simmons, Shipley and Park [4] have shown that such a diet stimulates osteoid production, and favors the production of "low phosphorus rickets" in the rat. The diet had this advantage in that it could be given *ad libitum*, the only essential being to cook the food as a mash, so that the animals could not pick out the components separately. The calcium and the phosphorus content

TABLE IV.

The calcium and phosphorus content of the serum of young dogs in January 29th, 1924, after nine weeks of Diet 2. (In mgms. per 100 c.c. serum.)

Dog	Calcium	Phosphorus	Product
No. 3*			
No. 4	10.4	2.7	28.0
No. 5	9.0	2.3	22.7
No. 6	9.5	2.5	23.7
No. 7	9.9	3.1	30.6
No. 8	9.5	2.4	22.8
No. 9	9.7	3.2	31.0
No. 10	10.1	2.6	26.0

* Died of distemper.

of the serum of these animals were studied weekly. The calcium remained fairly constant throughout the following weeks. The phosphorus showed a rather slow but constant decrease. The calcium and phosphorus content on January 29th, nine weeks after the diet was started, is given in Table IV.

Dogs 1 and 2 in which the bones of the foreleg were fractured on November 16th, were radiographed each week. At the end of four weeks in Dog 1, which was used as control, the bones had healed; in Dog 2, they were still ununited. Radiograms taken after four weeks revealed no evidence of healing in the case of Dog 2, whereas in Dog 1 the fracture was solidly united. These differences are clearly demonstrated in Plates 1, 2, 3 and 4.

On January 29, the bones of the right foreleg of Dogs 4, 5, 6, 7, 8, 9 and 10 were fractured. The calcium and the phosphorus content of their sera, in mgms. per 100 c.c., are given in Table IV. Dog 5 succumbed to the anesthesia. In these animals, as in those previously submitted to fracture, complete narcosis was obtained with ether, and both bones of the right foreleg were fractured. It is interesting to note that the bones were obviously more fragile and required less force to fracture them than did those of the normal animals. The bones were then immobilized in plaster, plates being taken before and after immobilization, in order to make certain that apposition was favorable for union of the fracture. The dogs were continued on Diet 2 as before. As a control series, five stock animals were submitted to similar fractures. These were kept on the regular laboratory diet, which contains ample phosphorus but scarcely any calcium. In order to make up for this deficiency, three grams of calcium carbonate were added to the daily ration. These fractures were immobilized in plaster just as for the dogs of the diet series. Analyses made of the sera at the time of fracture demonstrated that the calcium and the phosphorus content of the control series were normal. These control animals were examined chemically and radiographically each week. The calcium in these animals remained fairly constant throughout the study. No material increase in phosphorus was noted during the period of healing. Two weeks after fracture all five animals had callus and calcification. No false motion could be detected. All the animals, except Normal 1, used their fractured legs for weight-bearing. After three weeks healing was complete in all of the animals of the control series.

The diet series, on the other hand, presented a striking contrast. There was callus formation in all after two weeks, but no evidence whatsoever of calcification. This was demonstrable by the false motion at the site of fracture and by the radiogram. The radiographic evidence is shown in the accompanying plates 5 and 6, taken four weeks after fracture. An effort was made to take one plate with the lower fragment adducted and the other with it abducted in order to give an idea of the motion at the site of the fracture.

In order that the repair of fractures in the diet series animals which had a low serum phosphorus and a low product may be compared with that in the normal control animals, in which there was a normal relationship between the calcium and phosphorus, the radiograms of Dog 4, of the diet series, and of Normal 4, of the normal series are shown (Plates 7 and 8, respectively).

At the end of five weeks the fractures of the dogs in the diet series were still ununited, and there was still no evidence of calcification. Dog 2, in which a fracture had been produced much earlier than the others, had no evidence of union after three months. Two of the diet series animals in which the fractures had not united after six weeks were then placed on the diet of the normal series, a high phosphorus diet plus cod-liver oil. Healing was somewhat slower than in the normal animals, but as the product of the inorganic elements was raised, union occurred and was complete in five weeks. The remaining animals on Diet 2 still show no evidence of healing after eleven weeks.

Summary

This study of the healing of fractures in dogs on diets containing an adequate and an inadequate amount of calcium and phosphorus has brought out several interesting facts. The calcium and phosphorus product in the dog is much higher than in man. The calcium content is practically the same, that of phosphorus is much higher, being in general higher in the younger than in the older animals. It was also noted in this study that when dogs are placed on a deficient diet chemical changes are noted first in the serum of the older animals; the younger animals being much more refractory to dietary change. After a sufficient interval of time, however, the final result of the diet is the same in all the animals. The time necessary for observable change in the younger animals varied from four to six weeks. The time required for the reduction of the phosphorus to a point at which fractures would not unite was from nine to twelve weeks. Once the calcium and phosphorus product has been reduced and fractures made, non-union has invariably been the result. When these animals were again placed on an adequate dietary, healing resulted.

Conclusions

1. In the healing of fractures a definite relationship exists between the concentration of the inorganic bone-forming elements in the serum and the rate of repair.

2. If the phosphorus content of the blood serum of the dog is reduced by diet to such a degree that the product of the calcium and phosphorus is less than thirty, fractures will not unite.

Plate 1.—Dog 1 (on diet 1). Plate taken at time of fracture. Calcium 10, phosphorus 5.8, product 58.0.

Plate 2.—Dog 1 (on adequate diet). Plate taken four weeks after fracture. Calcium 10.3, phosphorus 5.6, product 57.7.

Plate 3.—Dog 2 (on diet 1). Plate taken at time of fracture. Calcium 8.9, phosphorus 3.6, product 32.0.

Plate 4.—Dog 2 (on diet 2) inadequate. Plate taken four weeks after fracture. Calcium 9.0, phosphorus 3.2, product 28.8.

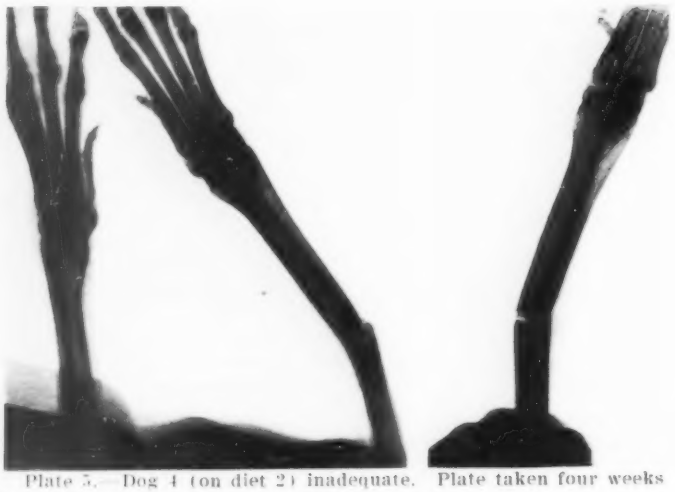

Plate 5.—Dog 4 (on diet 2) inadequate. Plate taken four weeks after fracture. Calcium 10, phosphorus 2.4, product 24.0.

Plate 6.—Dog 7 (on diet 2) inadequate. Plate taken four weeks after fracture. Calcium 9.8, phosphorus 2.7, product 26.5.

Plate 7.—Dog 4 (on diet 2). Plate taken four weeks after fracture. Calcium 10, phosphorus 2.4, product 24.0.

Plate 8.—Normal 4 (on adequate diet). Control animal to Dog 4. Plate taken four weeks after fracture. Calcium 10.2, phosphorus 5.7, product 58.1.

3. If the phosphorus and the calcium-phosphorus product are again raised to their normal level, the fractured bones will unite.

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NOTES ON NEW BOOKS

Clinical Aspects of the Electrocardiogram. A Manual for Physicians and Students. By HAROLD E. B. PARDEE, M. D. $4.00. *(New York, Paul B. Hoeber, Inc., 1924.)*

There is in this field a rapidly growing group of books which differ but slightly from one another. Dr. Pardee has endeavored to emphasize the clinical significance of the various abnormalities of the electrocardiogram. Unfortunately, many of the current conclusions in this regard rest entirely upon statistical studies, and in the last analysis must be said to derive their strength from the presence of pathological findings of a purely clinical order. It does not seem sound, for example, to build up a system of clinical interpretations of abnormalities of the T wave, as long as the nature of this wave is entirely unknown. The dependence of electrocardiographic changes upon functional disturbances, while not overlooked, is not sufficiently emphasized.

The treatment of the arrhythmias is satisfactory but adds little to what is already available.

The introductory chapter and the chapters on the normal electrocardiogram, the theory of the electrocardiogram and the description of the apparatus, are excellent, the last supplying a real deficiency in the literature. Provided too much reliance is not placed upon the clinical interpretation of the minor abnormalities of the form of the waves, this book may be highly recommended. F. R. D.

Abt's Pediatrics. Edited by ISAAC A. ABT, M. D. In eight octavo volumes totalling 8000 pages with 1500 illustrations, and separate Desk Index Volume. Vol. I, II, and III. $10.00 per volume. *(W. B. Saunders Co., Phila., 1923-1924.)*

The recent appearance of Abt's System of Pediatrics, a work that was begun during the turmoil of the World War, represents a mile-stone in the development of pediatrics in America. This system which is to appear in eight volumes, of which three have already been published, represents the efforts of one hundred and fifty contributors, including the editor, and promises to be the most exhaustive treatise on the subject. Volume I deals with the history of pediatrics, heredity, the anatomy of the child, growth, development, metabolism, physiology and hygiene. Volume II contains chapters on the factors which influence infant mortality, methods of diagnosis and examination of children, prophylaxis and treatment, the care of the newly born and of the premature infant, the bacteriology, chemistry and handling of milk, maternal and artificial feeding, disorders of metabolism, constitutional diatheses and the diseases due to food deficiencies. Volume III treats of gastro-intestinal physiology, nutritional disturbances, diseases and malformations of the mouth, tongue, nose, pharynx, teeth, diseases of the liver, pancreas, upper and lower respiratory tract including pneumonia.

The history of pediatrics is comprehensively and interestingly discussed by Garrison. The article by Murlin on the Physiology of Metabolism in Infancy and Childhood should serve as a valuable source of information for those planning original work in this field. In Robertson's article on Growth and Development, one cannot escape from the feeling that the mathematical treatment of the subject might have been omitted. It is difficult to understand why the chapter by Brenneman dealing with the management of difficult feeding cases should have been labelled "Growth and Development." We are in agreement with this author when he advises the early addition of orange juice, cod-liver oil and cereals to infants' diets. Although scurvy is uncommon before the sixth month we have seen cases develop several months earlier. Frank manifestations of scurvy do not appear in less than six weeks after all anti-scorbutic food is withdrawn, these manifestations representing the explosive end results of a slowly developing process. Except in children that have already suffered from a gastro-intestinal disturbance we have never seen harm follow the administration of orange juice. The gastro-intestinal tolerance of the normal infant is really tremendous and the exclusion of essential articles of diet, such as orange juice, cereals, eggs, is not justified either in theory or experience.

The chapter on the Constitutional Diatheses of childhood is an echo of by-gone days. In a brief article Marriott summarizes the present knowledge of coeliac disease and makes some very valuable suggestions as to its treatment. Abt's efforts to harmonize the various classifications of the nutritional disturbances of infants and children are, to say the least, very commendable.

One of the very excellent features of this work is the bibliography at the end of each chapter, arranged according to subjects. The work should be a valuable guide to the general practitioner and the pediatrician in hospital and private practice. It will simplify the work of the teacher and enable the investigator to tell almost at a glance how little is actually known regarding the problem he proposes to study. For this we can be thankful to Dr. Abt, the editor, for his courage in undertaking what must have been a tremendous task and to those who have aided and are aiding him in its fulfillment, including the publishers. B. K.

Text-book of Psychiatry. By PROF. DR. EUGEN BLEULER, Zurich. Authorized English Ed., by A. A. BRILL. 1924, 8°, 635 pp. $6.00. *(The Macmillan Company, New York.)*

The publication of a translation of Bleuler's "Text-book of Psychiatry" makes his views for the first time readily accessible (as far as text-book presentation will allow) to English-speaking students and practitioners. In the translator's preface and in the introduction by Kirby, principal stress is laid on the linkage of the formal Kraepelinian with the psychodynamic Freudian method in the description and elucidation of mental disease. A more distinctive interest attaches, however, to the conceptions that are more peculiarly Bleuler's, namely, "schizophrenia," and the classification of certain syndromes, including paranoia, in the "psychopathic reaction forms." As is well known, there are for Bleuler not one but many schizophrenias, among which the natural divisions are as yet obscure. He prefers the term "schizophrenia" in preference to "dementia praecox," partly because he recognizes the possibility of arrest and even of recovery to a considerable degree, and that the disease does not always appear at puberty or soon afterwards, and partly because of his own conceptions of its fundamental nature. These conceptions are, briefly and principally, "splitting" of the psychical functions and "autism." By "splitting" he means that two mental processes, mutually exclusive in the normal person, may exist side by side in the schizophrenic. In the emotional field, love and hatred for the same person may co-exist, without mutual interference (affective ambivalence). In the sphere of volition, an action may be performed in the presence of a tendency to the contrary (ambi-tendency); while in intellectual processes, opposing ideas may have equal value (ambivalency). "Autistic thinking," of which day-dreaming is a variety, ignores contradictions

with reality, and in schizophrenia it goes so far as to allow the most absurd associations to go uncorrected.

In the psychopathies, Bleuler includes psychic deviations from the normal which do not amount to pronounced insanity, but in which affective anomalies are outstanding. Upon the basis of any such psychopathic disposition, a difficult situation may produce outspoken symptoms of various kinds, which may disappear with the disappearance of the environmental difficulty. These are the "psychopathic forms of reaction"—symptom-groups released from the underlying disposition. It is the abnormal affectivity, associated with a sense of inferiority and with a maladjustment of the understanding and affectivity that is supposed (although admittedly the explanation is incomplete) to produce paranoia.

Interesting also are the conceptions of syntonic and schizoid types of disposition, especially in relation to the inheritance of mental disorders.

It is to be regretted that such a sensible presentation of psychiatric knowledge should suffer in translation. Only a few of the many errors can be mentioned here. "Wahn" and "Wahnsinn" are repeatedly mistranslated with misleading results (e. g. p. 207—"mania" instead of delusional insanity, for "Wahnsinn"). The persistent mistranslation of "Empfindung" by "feeling" (e. g. pp. 56 and 57) is a glaring error in elementary psychology. There is more than one barbarous rendering of this sort:—"To assert oneself or the genus (sic) in accordance with the aim of the psychic apparatus . . . . is expressed in every psychism in a tendency to react" (p. 50). Luckily most readers will hesitate before accepting "brain inflammation" as a cause of schizophrenia. This is the translator's rendering of "Hirnschwellung" (Rieger). Errors in English, as well as in punctuation, lead to such amusing statements as that "a prison psychosis" may be the reaction to "a confinement." Imperfect proof-revision produces curious dicta such as "writing predisposes language" (for "presupposes") and sometimes even the reverse of the author's meaning is conveyed (p. 62)—"impugnable" for "unimpugnable" and (p. 113) "clear"for "unclear." It is to be hoped that such errors will be corrected in a future edition. R. D. G.

Diseases of the Skin. By RICHARD L. SUTTON, M. D., LL.D. 5th Edition. $10.00. *(St. Louis, C. V. Mosby, 1923.)*

The book has been enlarged—and to material advantage; this was necessary in order to include a number of rare conditions which in recent years have found their way into the literature. There has been apparently no change in the general presentation of the subject: perhaps the author is biding his time before attempting a classification of the diseases along etiological lines; but we hope to see something of this kind in the future from the pen of one whose contributions usually attest to a vigor of mind and to a sharp, critical attitude.

His style and clarity of presentation have been carried over into his textbook. The subject matter is arranged in much the manner found in other textbooks of similar size and scope, which naturally militates against perfection. For example, there is no adequate mention of such a condition as lichenification; or a special stressing of the conditions or diseases of the skin associated with it, e. g., lichen simplex chronicus, (neurodermatosis), etc. As with most other authors the important subjects of dermatitis and eczema are still left in the limbo of uncertainty, which is always a source of confusion and misunderstanding, and Sutton still considers eczema a "sort of dermatological scrapheap out of which, from time to time, certain diseases that present a characteristic and definite symptomatology are extracted."

Nevertheless, there is so much to commend that attention may well be directed, among other points, to the chapter on diagnosis and especially to that on classification. The addition of a well arranged and annotated bibliography for most subjects is very acceptable and valuable. The stressing of pathology is entirely adequate; and the handling of therapy is most commendable, inasmuch as the author is both generous in citing the experience of others as well as expressing frankly his own views,—the very thing which distinguishes a book. To us, however, the most striking attraction is the lavish presentation of photographs which are not only faithful and beautiful representations of skin diseases by many other workers in this field as well as by himself, but also so typical and so well selected that they go far to make the subject matter more vivid, impressive and instructive.

The book is remarkably free from typographical errors; the subject headings and the selection of type allow of rapid and easy reference; and the size is adequately handy. We heartily recommend it to the casual reader and to the teacher for their individual needs. I. R. P.

Surgical Emergencies. RUSSELL HOWARD, C. B. E., M. S., F. R. C. S $2.50. *(New York, Longmans, Green & Co., 1924.)*

This little book is, as it purports to be, a compact, fairly complete outline of true surgical emergencies most likely to be met with, together with the more important points of differential diagnosis and a bare suggestion of the treatment. One can readily see its use in the small hospital where no skilled surgeon is immediately available, and where the general practitioner must fill in the breach; to do so he must have some condensed compendium of possibilities with which to brush up his memory and bolster up his judgment. For such use, it would seem not to have been amiss to have included a somewhat more detailed and comprehensive outline of the surgical principles and operative steps involved—they seem to be left so vague as to be somewhat confusing in spots; and certainly would not be of great help to one who was, at best, rather unfamiliar with operative procedures.

The section on the recognition and diagnosis of the surgically acute abdomen strikes one as the particularly bright spot in the book; the general advice, and more especially the "don'ts," should be most helpful to the average general practitioner.

On the whole, the book should have a place in the library of anyone liable to be called upon in an emergency, but should prove particularly useful to the man, who, in a small community, must fill the multiplicity of rôles allotted singly to the various specialists in a larger town or city. J. M. T. F., Jr.

War Blindness at St. Dunstan's. By SIR ARNOLD LAWSON. 148 pp. $2.50. *(Oxford Medical Publications, London, 1922.)*

This book presents a very interesting discussion of Great Britain's problem with the war-blinded. It is divided into three parts, the first dealing with the medical aspect of the traumatically blind. The second part deals similarly with the medical aspect of the non-traumatically blind, or the ocular complications of general disease. Both of these parts are completely illustrated by summaries of case histories. The third portion of the book deals with the social problems related to the blind, especially those who lose their sight in adult life. The pension system is described, and the question of re-education discussed.

The most striking impression one gathers from this interesting book is the similarity of the situation in England to that in America. Both along the medical and social phases,

one finds the same problems and the same errors. Inasmuch as St. Dunstan's was established in the closing months of 1914, and the Evergreen School for the Blind, the American analogue of St. Dunstan's, was established in 1918, one would imagine that a considerable number of the errors inevitable in the establishment of the first institution might well have been avoided in the second. In some instances this is undoubtedly true, yet in others we find the same mistakes. In *War Blindness at St. Dunstan's*, we read of the confusion surrounding the treatment and pensioning of those blinded from syphilis, congenital or acquired. The story is told of over one hundred patients who have lost their sight either from interstitial keratitis or central nervous system lues, on the re-education of whom the government spends large sums, while apparently not one penny is spent in the treatment of the underlying condition. Similarly the tragic story is told of men gradually but surely losing their vision from cerebral neoplasms, where apparently the only therapeutic procedure has been a fruitless decompression. Such instances would be easy to criticize, did we not know that in many cases they find their parallel in our own country several years later. Yet in the main, it is impossible to read this book without great admiration for St. Dunstan's, and the humane understanding of those in charge.

This story is well and simply told. It is not written primarily for the specialist, but will afford an interesting and profitable evening's reading for any physician, or for anyone interested in the problems of the blind. A. C. W.

Manual of the Diseases of the Eye. By CHARLES H. MAY. 11th Edition. $4.00. *(Wm. Wood and Co., New York, 1924.)*

That Dr. May's treatise has gained an immense popularity is proved by the fact that it has now reached the enormous sale of one hundred and fifty thousand copies. It is intended primarily for students, very complete in its general plan, and equally brief in its discussion of individual conditions. The study of this manual will undoubtedly enable any medical student to pass any undergraduate or State Board examination that the average examiner would feel justified in giving. It is also probable that such a student would emerge from its perusal with little or no conception of the broader principles and problems of the specialty the book purports to cover, and with little idea of the relationship of ocular disorders to internal medicine. There is probably need, however, for brief introductory treatises of this type, and of its kind, this manual is among the best. A. C. W.

Heliotherapy. By A. ROLLIER. 288 pp. $8.00. *(Oxford Medical Publications, Henry Frowde and Hodder and Stoughton, London, 1923.)*

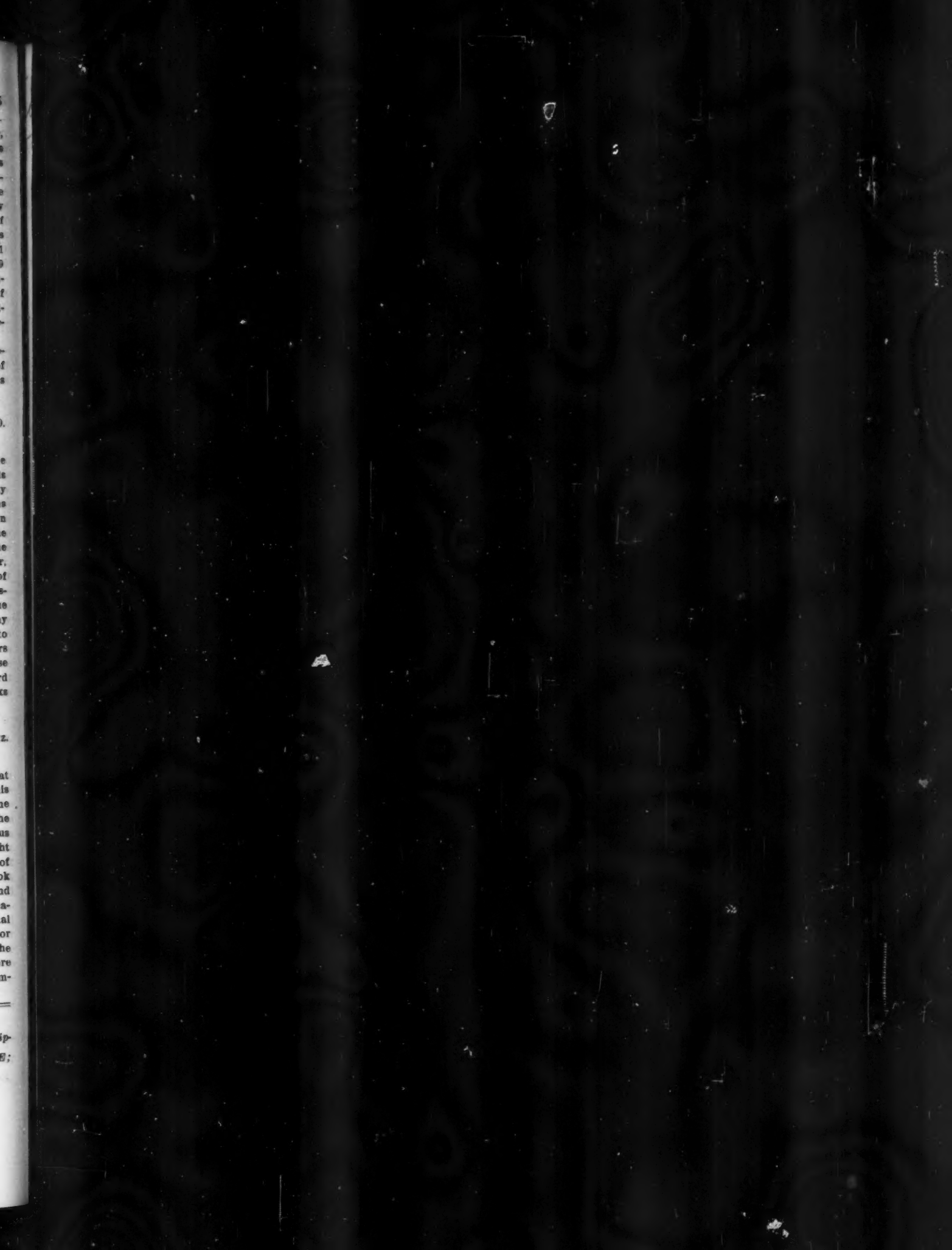
Heliotherapy has come to hold a prominent and, in all probability, a worthy place in the treatment of tuberculosis, and in this book Rollier, who has done so much to advance the theme and method of sun-cure, explains concisely what are the effects of the sun-bath upon the skin and upon disease, deals with the technique of exposure, and presents the results of more than twenty years' experience with this mode of treatment in all types of tuberculosis. There is a good discussion on tuberculosis of practically all parts of the body and a discussion of the results of regional heliotherapy. The work is tinctured with considerable enthusiasm, which, however, seems to be warranted in large measure by case reports. There is an over-emphasis of the significance of secondary infections which transform "cold abscesses into hot abscesses." Of considerable interest is the postural treatment which enables the patient to develop sufficient muscle while taking it to justify the disuse of casts for spinal caries. Care of contacts and of children with localized tuberculosis in open-air schools is described and statistics covering the years from 1903 to 1921 show an astonishingly high proportion of "healing." Of 1129 patients up to 1913, in 945 healing took place, 112 were improved, in 41 the disease remained stationary and 31 died. Of 2167 cases (bones and joints) from 1913 to 1921, in 1746 healing took place, in 242 improvement, in 147 the disease remained stationary and in 32 became worse.

There is a detailed discussion of the scientific basis of heliotherapy, and a consideration of radiological diagnosis and of the use of sunlight in nontuberculous diseases. The work is interesting, stimulating and on the whole well done. H. S. W.

Recovery Record. By G. B. WEBB and C. T. RYDER. 185 pp. $2.00. *(Paul B. Hoeber, New York, 1923.)*

Although the burden of the cure is upon the patient, the latter needs occasional advice from the physician, and this little volume aims to be a guide-book. An exposition, in lay language and definition, of some of the conspicuous symptoms and incidental complaints, the book includes a dissertation upon the hygiene of recovery and advises the patient as to the significance of the temperature and pulse reactions, the technique of taking and recording each, of diet and fresh air, of keeping warm, of protecting others, of regular habits, of amusements, of simple care of constipation, anorexia, nervousness, sleeplessness, headache, hemorrhage and other true symptoms, of avoiding colds, etc. In addition to the many helpful suggestions to patients which should enable them to understand much more rationally their sickness, the authors have added some one hundred pages of temperature and pulse charts, which will furnish the patient with an individual record book. Quotations from the classics and from modern works on tuberculosis embellish the chart pages. H. S. W.

Nervous and Mental Re-education. By SHEPHERD IVORY FRANZ. *(New York, The Macmillan Company, 1923.)*

From the days of his association with Dr. August Hoch at the McLean Hospital, Waverly, Mass., Dr. Franz turned his psychological interest to the re-education of aphasics. At the Government Hospital for the Insane, Washington, D. C., he organized training for victims of hemiplegia and other nervous diseases. During and since the war his experience was brought to bear on the war cases and on courses for the training of physicians. Out of this experience Dr. Franz gives us a book highly creditable to a psychologist, covering the basis and general concept of re-education (pp. 3-48), general re-education principles (pp. 49-130), and the neurological and mental adjustments (pp. 131-222): anterior poliomyelitis, locomotor ataxia, cerebral palsies, speech defects and the psychotic. The book deals with principles and results and is not a mere directory of cut and dried methods and should be a very commendable help. A. M.

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